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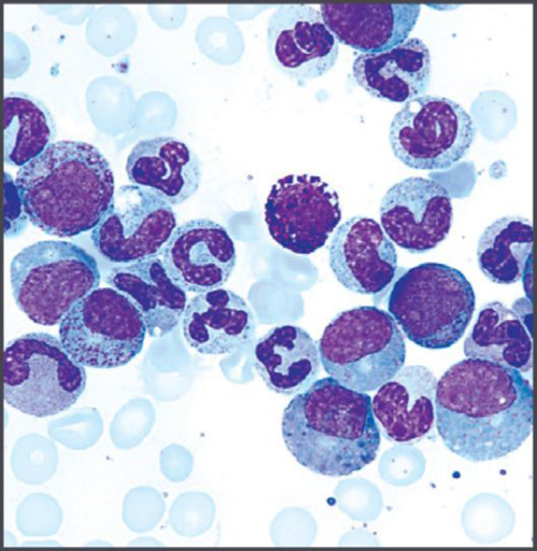

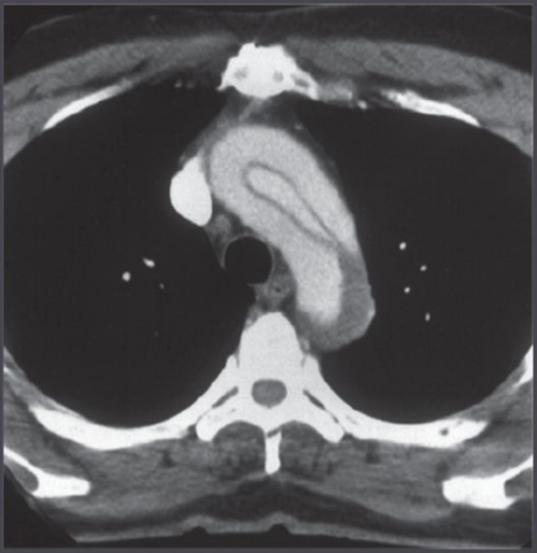

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The authors, editors, and publisher have exerted efforts to ensure that drug selection and dosage set forth in this text are in accordance with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, readers are urged to check the package insert for each drug for any change in indications and dosage and for added wordings and precautions. This is particularly important when the recommended agent is a new or infrequently employed drug.

Some drugs and medical devices presented in this publication have US Food and Drug Administration (FDA) clearance for limited use in restricted research settings. It is the responsibility of the health care providers to ascertain the FDA status of each drug or device planned for use in their clinical practice.

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To my mentors Drs Thomas J. Beckman and Paul S. Mueller for their endless support, inspiration, and wisdom.

Christopher M. Wittich, MD, PharmD

Foreword

Publication of the *Mayo Clinic Internal Medicine Board Review*, Twelfth Edition, coincides with important milestones for the Department of Medicine at Mayo Clinic, including the department's inception 50 years ago and the 25th anniversary of this book. Providing medical education across the training continuum has been a part of the Department of Medicine's primary mission since the beginning. The department has robust medical education programs for medical students, residents, fellows, and physicians in practice. The *Mayo Clinic Internal Medicine Board Review* is an example of the department's dedication to lifelong learning by internal medicine physicians.

The current edition builds on years of knowledge, refinement, and expertise from the Department of Medicine. Chapters have been revised to include the most up-to-date knowledge for the practice of medicine. Two entirely new chapters on physician well-being and hospital internal medicine emphasize the importance of those areas to the practice of internal medicine. All the authors are Mayo Clinic experts primarily focused on caring for patients, and the editors are experienced internists who are expert diagnosticians and medical educators.

This textbook will be an important resource for anyone preparing to become certified in internal medicine or seeking to provide state-of-the-art care to patients.

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Preface[a]

The *Mayo Clinic Internal Medicine Board Review*, Twelfth Edition, is the result of the dedicated efforts of Mayo Clinic physicians in multiple specialties whose primary mission is to put the needs of the patient first. The field of internal medicine is constantly changing as science is advanced, and this textbook was written to provide readers with the essential elements for the practice of internal medicine. Readers preparing for the American Board of Internal Medicine (ABIM) Certification and Maintenance of Certification examinations will find the textbook comprehensive and easy to study. Additionally, readers who want a reference or a general knowledge review in internal medicine will find this textbook an important addition to their medical library.

The Twelfth Edition features revised chapters that highlight current knowledge in the practice of internal medicine. Additionally, this edition includes over 200 new multiple-choice questions designed to underscore key teaching points. Each question includes a rationale in a standard format that describes why the correct answer is right and why each incorrect answer is wrong. This edition includes color-coded section tabs, and within each chapter, key facts and key definitions are highlighted separately from the main text to improve knowledge retention. New chapters have been added on physician well-being and hospital internal medicine. The goal was to create a book that is comprehensive, useful, and easy to study.

I wish to thank all the authors for their depth of knowledge and dedication to making this edition clinically relevant and state-of-the-art. I am especially grateful to the associate editors, Thomas J. Beckman, MD, Sara L. Bonnes, MD, Nerissa M. Collins, MD, Nina M. Schwenk, MD, Christopher R. Stephenson, MD, and Jason H. Szostek, MD, who are all outstanding general internists and medical educators. I would like to thank Amy W. Williams, MD, Chair of the Department of Internal Medicine at Mayo Clinic in Rochester, Minnesota, and Karthik Ghosh, MD, Chair of the Division of General Internal Medicine, who provided the resources to make this textbook a success. I also thank Michael W. O'Brien for his administrative support. This book would not exist without the dedication of the Mayo Clinic Scientific Publications staff, including Joseph G. Murphy, MD, Chair; Randall J. Fritz, DVM, Alyssa B. Quiggle, PhD, Colleen M. Sauber, MEd, and LeAnn M. Stee, editors; Kenna L. Atherton, manager; Kristin M. Nett and Emelina R. Bly, editorial assistants; and John P. Hedlund, proofreader. I gratefully acknowledge the support of Mayo Clinic Scientific Press and Oxford University Press. Finally, I thank Laura M. Sadosty, in the Department of Medicine, who organized over 90 physician authors—a remarkable feat indeed!

In the spirit of the previous editions, I trust that *Mayo Clinic Internal Medicine Board Review,* Twelfth Edition, will serve those in the pursuit of mastering the art and science of internal medicine.

Christopher M. Wittich, MD, PharmD

Editor-in-Chief

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[a] Cover images (selected to illustrate the breadth of knowledge required to be an internist), clockwise from the left: Figure 26.18. dermatomyositis: Gottron papules; Figure 41.8. chronic myeloid leukemia; Figure 11.7C. computed tomogram showing aortic dissection.

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Section I

Allergy

1 Allergic Diseases[a]

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Allergic diseases include atopic or immunoglobulin E (IgE)–mediated disorders that classically involve allergic rhinoconjunctivitis, allergic asthma, food and medication allergy, and anaphylaxis. Although not mediated by IgE, certain diseases are often grouped with allergic diseases and include eosinophilic diseases, mast cell disease, nonallergic rhinitis, chronic rhinosinusitis, and primary immunodeficiency.

Allergy Testing

Standard allergy testing relies on identifying IgE antibody specific for the allergen in question. Two classic methods of doing this are the immediate wheal-and-flare skin prick tests (in which a small amount of antigen is introduced into the skin and the site is evaluated after 15 minutes for the presence of an immediate wheal-and-flare reaction) and in vitro (blood) testing.

Methods of allergy testing that do not have a clear scientific basis include cytotoxic testing, provocation-neutralization testing or treatment, and yeast allergy testing.

Patch Tests and Skin Prick Tests

Patch testing of skin is not the same as immediate wheal-and-flare skin prick testing. Patch testing is used to investigate only contact dermatitis, a type IV hypersensitivity skin reaction. Patch tests require 72 to 96 hours for complete evaluation. Many substances cause contact dermatitis. Common contact sensitivities include those to nickel, formaldehyde, fragrances, and latex.

Skin prick testing, by comparison, identifies inhalant allergens that cause respiratory symptoms, such as allergic rhinitis and asthma. These allergens include dust mites, cats, dogs, cockroaches, molds, and pollen of trees, grass, and weeds. Food allergy is also assessed with skin prick testing.

Skin prick testing and intradermal testing involve introducing allergen into the skin layers below the external keratin layer. Intradermal testing, the deeper technique, is used to evaluate allergy to stinging insect venoms, penicillin, and other medications. Intradermal tests are preceded by skin prick tests.

Drugs with antihistamine properties, such as histamine$_1$ (H_1) receptor antagonists, and many anticholinergic and tricyclic antidepressant drugs can suppress the immediate response to allergy skin tests. Use of nonsedating antihistamines should be discontinued 5 days before skin testing. Histamine$_2$ (H_2) receptor antagonists have a small suppressive effect. High-dose corticosteroid treatment can suppress the delayed-type hypersensitivity and the immediate response.

In Vitro Allergy Tests

In vitro (blood) allergy testing initially involves chemically coupling allergen protein molecules to a solid-phase substance and ultimately measuring the patient's IgE specific to the allergen through radiolabeling, colorimetry, or other markers.

This test identifies the presence of allergen-specific IgE antibody in the same way that the allergen skin test does. Generally, in vitro allergy testing is not as sensitive as skin testing and has limitations because of the potential for chemical modification of the allergen protein while it is being coupled to the solid phase. Generally, in vitro allergy testing is more expensive than allergen skin tests and has no advantage in routine clinical practice. The

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[a] Portions previously published in Volcheck GW. Clinical allergy: diagnosis and management. Totowa (NJ): Humana; c2009; used with permission of Mayo Foundation for Medical Education and Research.

Table 1.1 • Allergy Test Types, Uses, and Considerations

Test Type	How Performed	Used to Diagnose	Notes
Skin prick test	Skin prick, read in 15 minutes	Airborne, food, medication, venom	Current use of antihistamines or a clinically significant underlying skin condition interfere with test
Skin intradermal test	Placed just under skin, read in 15 minutes	Medication, venom	Low specificity for airborne; potentially dangerous for food
In vitro specific IgE	Blood test, result availability depends on laboratory	Airborne, food, venom	In general, more costly and less sensitive than skin testing
Patch test	Patches placed on back, left for 48 hours, read over 72 to 96 hours	Contact sensitivity on the skin	Not to be confused with the other forms of allergy testing

Abbreviation: IgE, immunoglobulin E.

test may be useful clinically for patients who have been taking antihistamines and are unable to discontinue their use or for patients who have primary cutaneous diseases that make allergen skin testing impractical or inaccurate (eg, severe atopic eczema with most of the skin involved in a flare).

Table 1.1 summarizes the tests and considerations for their use.

Chronic Rhinitis

Medical History

The differential diagnosis of chronic rhinitis is given in Box 1.1. **Nonallergic rhinitis** is defined as nasal symptoms occurring in response to nonspecific, nonallergic irritants. Vasomotor rhinitis is the most common form. Common triggers of vasomotor rhinitis are strong odors, respiratory irritants such as dust or smoke, changes in temperature, changes in body position, and ingestants such as spicy food or alcohol.

Box 1.1 • Differential Diagnosis of Chronic Rhinitis

- Bilateral presentation
  - Allergic rhinitis
  - Vasomotor rhinitis
  - Rhinitis medicamentosa
  - Sinusitis
- Unilateral presentation
  - Nasal polyposis
  - Nasal septal deviation
  - Foreign body
  - Tumor

Key Definition

Nonallergic rhinitis: *nasal symptoms occurring in response to nonspecific, nonallergic irritants.*

Historical factors favoring a diagnosis of *allergic* rhinitis include a history of nasal symptoms that have a recurrent seasonal pattern (eg, every August and September) or symptoms provoked by being near specific sources of allergens, such as animals. Factors favoring a diagnosis of *vasomotor* rhinitis include symptoms provoked by strong odors and changes in humidity and temperature.

Factors common to allergic rhinitis and nonallergic rhinitis (thus, without differential diagnostic value) include perennial symptoms, intolerance of cigarette smoke, and history of “dust sensitivity.” Factors suggestive of fixed nasal obstruction (which should prompt physicians to consider other diagnoses) include unilateral nasal obstruction, unilateral facial pain, unilateral nasal purulence, nasal voice but no nasal symptoms, disturbances of olfaction without any nasal symptoms, and unilateral nasal bleeding. Nasal polyps, septal deviation, and tumor may present with unilateral symptoms. Further evaluation with computed tomography (CT) of the sinuses or rhinolaryngoscopy is indicated.

Allergy Skin Tests in Allergic Rhinitis

Interpretation of allergy skin test results must be tailored to the unique features of each patient. For patients with perennial symptoms and negative results on allergy skin tests, the diagnosis is nonallergic rhinitis. For patients with seasonal symptoms and appropriately positive results on allergy skin tests, the diagnosis is seasonal allergic rhinitis. For patients with perennial symptoms, positive results on allergy skin tests for house dust mite suggest house dust mite allergic rhinitis. In this case, dust mite allergen avoidance should be recommended.

Corticosteroid Therapy for Rhinitis

The need for systemic corticosteroid treatment of rhinitis is limited. Occasionally, patients with severe symptoms of allergic rhinitis may benefit greatly from a short course of prednisone (10 mg 4 times daily by mouth for 5 days). Improvement may be sufficient to allow topical corticosteroids to penetrate the nose and satisfactory levels of antihistamine to be established in the blood. Severe nasal polyposis, a separate condition, may warrant a longer course of oral corticosteroid therapy. Sometimes, recurrence of nasal polyps can be prevented by continued use of topical corticosteroids. Polypectomy may be required if nasal polyps do not respond to treatment with systemic and intranasal corticosteroids, but nasal polyps often recur after surgical intervention.

In contrast to systemic corticosteroids, topical corticosteroid agents for the nose are easy to use and have few adverse systemic effects.

KEY FACTS

- ✓ Patch testing—used to investigate only contact dermatitis
- ✓ Skin prick testing—identifies inhalant allergens that cause respiratory symptoms
- ✓ Nasal symptoms with a recurrent seasonal pattern—favor a diagnosis of allergic rhinitis
- ✓ Intranasal corticosteroids—easy to use; few adverse systemic effects

Long-term treatment with decongestant nasal sprays may have potential for abuse—a vicious cycle of rebound congestion called *rhinitis medicamentosa* caused by topical vasoconstrictors. In contrast, intranasal corticosteroid therapy does not induce this type of treatment dependence.

A substantial number of patients with nonallergic rhinitis also have a good response to intranasal (topical aerosol) corticosteroid therapy, especially if they have the nasal eosinophilia form of nonallergic rhinitis.

A patient who has allergic rhinitis and does not receive adequate relief with topical corticosteroid plus antihistamine therapy may need systemic corticosteroid treatment and immunotherapy.

An unusual adverse effect of intranasal corticosteroids is nasal septal perforation. Spray canisters deliver a powerful jet of particulates, and a few patients have misdirected the jet to the nasal septum. Instruction on correct nasal inhaler technique can help in prevention.

Antihistamines and Other Treatments

Antihistamines antagonize the interaction of histamine with its receptors. Histamine may be more causative of nasal itch and sneezing than other mast cell mediators. These are the symptoms most often responsive to antihistamine therapy.

Pseudoephedrine is the most common decongestant agent in nonprescription drugs for treating cold symptoms and rhinitis and usually is the active decongestant agent in widely used prescription agents. Phenylpropanolamine has been removed from the market because of its association with hemorrhagic stroke in women. Several prescription and nonprescription combination agents combine an antihistamine and a decongestant. Saline nasal rinses may provide symptomatic improvement in patients with chronic rhinitis by helping to remove mucus from the nares.

In men who are in middle age or are older, urinary retention may be caused by antihistamines (principally the older drugs that have anticholinergic effects) and decongestants. Although there has been concern for years that decongestants may exacerbate hypertension because they are α-adrenergic agonists, a clinically significant hypertensive response is rare in patients with hypertension that is controlled medically.

Immunotherapy for Allergic Rhinitis

Until topical nasal glucocorticoid sprays were introduced, allergen immunotherapy was considered first-line therapy for allergic rhinitis when the relevant allergen was seasonal pollen of grass, trees, or weeds. Immunotherapy became second-line therapy after topical corticosteroids were introduced, because immunotherapy requires a larger time commitment during the build-up phase and carries a small risk of anaphylaxis due to the immunotherapy injection itself. However, immunotherapy for allergic rhinitis can be appropriate first-line therapy for selected patients and is highly effective.

Immunotherapy is often reserved for patients who do not receive satisfactory relief from intranasal corticosteroids or who cannot tolerate antihistamines. Controlled trials have shown a benefit for pollen, dust mite, and cat allergies and a variable benefit for mold allergy. Immunotherapy is not used for food allergy or nonallergic rhinitis. Immunotherapy has also been shown to decrease the prevalence of the development of asthma in children with allergic rhinitis and to decrease the onset of new allergen sensitivities in those treated for a single allergen.

Environmental Modification

House Dust Mites

The home harbors the most substantial dust mite populations in bedding, fabric-upholstered furniture (heavily used), and carpeting over concrete (when concrete is in contact with the ground). To decrease mite exposure, bedding (and sometimes, when practical, furniture cushions) should be encased in mite-impermeable encasements. To some degree, encasements also prevent infusion of water vapor into the bedding matrix. These 2 factors, a mite barrier and decreased humidity, combine to markedly decrease the amount of airborne mite allergen. In contrast, recently marketed acaricides that kill mites or denature their protein allergens have not proved useful in the home. Measures for controlling dust mites are listed in Box 1.2.

Box 1.2 • Dust Mite Control

Encase bedding and pillows in mite-impermeable encasements
Wash sheets and pillowcases in hot water weekly
Remove carpeting from bedroom
Remove upholstered furniture from bedroom
Use a dehumidifier

Pollen

Air conditioning, which enables the home to remain tightly closed, is the principal defense against pollinosis. Most masks purchased at local pharmacies cannot exclude pollen particles and are not worth the expense. Some masks can protect the wearer from allergen exposure. These are industrial-quality respirators designed specifically to pass rigorous testing by the US Occupational Safety and Health Administration and the National Institute for Occupational Safety and Health and to meet certification requirements for excluding a wide spectrum of particulates, including pollen and mold. These masks allow wearers to mow the lawn and do yard work, which would be intolerable otherwise because of sensitivity to pollen allergen. It is important to shower and change clothes when entering the home after spending substantial time outdoors during allergy season.

KEY FACTS

- ✓ Decongestant nasal sprays—used long term, may cause rebound congestion (rhinitis medicamentosa)
- ✓ Immunotherapy—became second-line therapy for allergic rhinitis after topical corticosteroids were introduced
- ✓ Dust mite populations—greatest in bedding, upholstered furniture, and carpeting over concrete
- ✓ Principal defense against pollinosis—air conditioning

Animal Dander

No measure for controlling animal dander can compare with complete removal of the animal from the home. If complete removal is not tenable, some partial measures must be considered. Recommendations include keeping the animal out of the bedroom entirely and attempting to keep the animal in 1 area of the home. A high-efficiency particulate air (HEPA) room air purifier should be placed in the bedroom. The person should avoid close contact with the animal and should consider using a mask when handling the animal or entering the room where the animal is kept. Bathing cats about once every other week may reduce the allergen load in the environment.

Box 1.3 • Complications of Sinusitis

Meningitis
Subdural abscess
Extradural abscess
Orbital infection
Cellulitis
Cavernous sinus thrombosis

Sinusitis

Sinusitis is closely associated with edematous obstruction of the sinus ostia (ostiomeatal complex). Poor drainage of the sinus cavities predisposes to infection, particularly by microorganisms that thrive in low-oxygen environments (eg, anaerobes). In adults, *Streptococcus pneumoniae, Haemophilus influenzae*, anaerobes, and viruses are common pathogens in cases of sinusitis. In addition, *Moraxella* (*Branhamella) catarrhalis* is an important pathogen in children.

Important clinical features of acute sinusitis are purulent nasal discharge, tooth pain, cough, and poor response to decongestants. Findings on paranasal sinus transillumination may be abnormal.

Physicians should be aware of the complications of sinusitis, which can be life threatening (Box 1.3). Untreated sinusitis may lead to osteomyelitis, orbital and periorbital cellulitis, meningitis, and brain abscess. Cavernous sinus thrombosis, an especially serious complication, can lead to retrobulbar pain, extraocular muscle paralysis, and blindness.

Mucormycosis can cause recurrent or persistent sinusitis refractory to antibiotics. Allergic fungal sinusitis is characterized by persistent sinusitis, eosinophilia, increased total IgE level, antifungal (usually *Aspergillus*) IgE antibodies, and fungal colonization of the sinuses. Granulomatosis with polyangiitis (Wegener), ciliary dyskinesia, and hypogammaglobulinemia are medical conditions that can cause refractory sinusitis (Box 1.4).

Box 1.4 • Causes of Persistent or Recurrent Sinusitis

Nasal polyposis
Mucormycosis
Allergic fungal sinusitis
Ciliary dyskinesia
Granulomatosis with polyangiitis (Wegener)
Hypogammaglobulinemia
Tumor

Chronic Sinusitis

Chronic sinusitis is considered primarily an inflammatory disease as opposed to an infectious disease. Although patients with chronic sinusitis are predisposed to an acute sinus infection, an infection is not the underlying cause of the chronic sinusitis. Chronic noninfectious sinusitis is most often due to eosinophilic inflammation of the sinus tissue with or without polyp formation. Treatment consists primarily of topical and systemic corticosteroids and saline irrigations. Some of these patients may have aspirin sensitivity manifest in the development of sinus or respiratory symptoms up to 3 hours after the use of a nonsteroidal anti-inflammatory medication. In this patient group, aspirin desensitization and leukotriene antagonists can also be beneficial. Sinus surgery can be helpful but is not curative, given the recurrent inflammatory component of this disease.

Persistent, refractory, and complicated sinusitis should be evaluated by a specialist. Rhinoscopy and sinus CT are the preferred studies for identifying the extent of the disease in these patients (Figure 1.1).

Amoxicillin (500 mg 3 times daily) or trimethoprim-sulfamethoxazole (1 double-strength capsule twice daily) for 10 to 14 days is the treatment of choice for uncomplicated maxillary sinusitis.

Plain radiography of the sinuses is less sensitive than CT (using the coronal sectioning technique). CT shows greater detail about sinus mucosal surfaces, but CT usually is not necessary in acute, uncomplicated sinusitis. CT is indicated, however, for patients for whom a sinus operation is being considered and for those for whom standard treatment of sinusitis fails. Yet, patients with extensive dental restorations that contain metal may generate too much artifact for CT to be useful. For these patients, magnetic resonance imaging techniques are indicated.

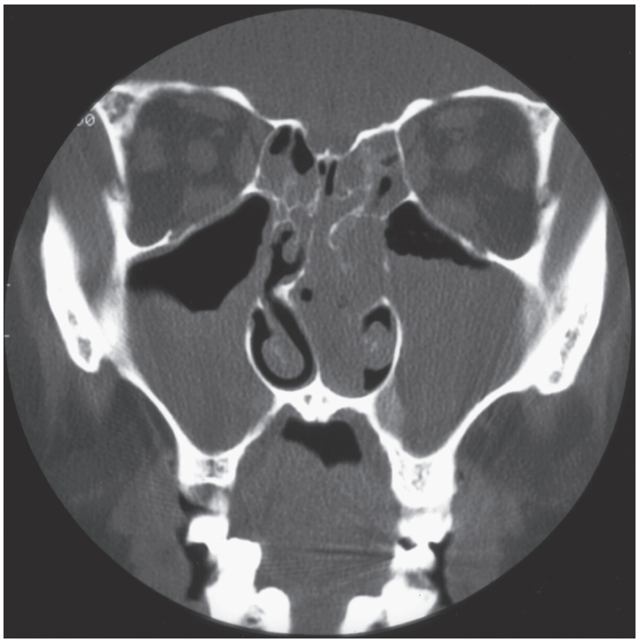

Figure 1.1. *Sinusitis. Sinus computed tomogram shows opacification of the osteomeatal complex on the left, subtotal opacification of the right maxillary sinus, and an air-fluid level in the left maxillary antrum.*

KEY FACTS

- ✓ Common sinusitis pathogens in adults—*Streptococcus pneumoniae, Haemophilus influenzae*, anaerobes, and viruses
- ✓ Clinical features of acute sinusitis—purulent nasal discharge, tooth pain, cough, and poor response to decongestants
- ✓ Chronic noninfectious sinusitis—usually due to eosinophilic inflammation with or without polyps
- ✓ Amoxicillin or trimethoprim-sulfamethoxazole—therapeutic choice for uncomplicated maxillary sinusitis

Urticaria and Angioedema

Duration of Urticaria

The distinction between *acute urticaria* and *chronic urticaria* is based on duration. If urticaria has been present for 6 weeks or longer, it is called *chronic urticaria*.

Secondary Urticaria

In most patients, urticaria is simply a skin disease (*chronic idiopathic urticaria*). Many of these patients have an antibody that interacts with their own IgE or IgE receptor and produces the urticaria. Occasionally, urticaria is the presenting sign of more serious internal disease. It can be a sign of lupus erythematosus and other connective tissue diseases, particularly the "overlap" syndromes that are more difficult to categorize. Thyroid disease, malignancy (mainly of the gastrointestinal tract), lymphoproliferative diseases, and occult infection (particularly of the intestines, gallbladder, and dentition) may be associated with urticaria. Immune complex disease has been associated with urticaria, usually with urticarial vasculitis; hepatitis B virus has been identified as an antigen in cases of urticaria and immune complex disease.

A common cause of acute urticaria and angioedema (other than the idiopathic type) is drug or food allergy. However, drug or food allergy usually does not cause chronic urticaria.

Relationship Between Urticaria and Angioedema

In common idiopathic urticaria, the hives last 2 to 18 hours, and the lesions itch intensely because histamine is the primary cause of wheal formation.

The pathophysiologic mechanism is similar for urticaria and angioedema. The critical factor is the type of tissue in which the capillary leak and mediator release occur. Urticaria develops when the capillary events are in the tissue wall of the skin, the epidermis. Angioedema occurs when the capillary events affect vessels in the loose connective tissue of the deeper layers that make up the dermis. Virtually all patients with common idiopathic urticaria also have angioedema at some point.

Hereditary Angioedema

Hereditary angioedema (HAE), a rare genetic condition due to C1 esterase inhibitor dysfunction, is characterized by recurrent episodes of angioedema, typically without urticaria. The duration, size, and location of individual swellings vary. Many patients with HAE have also had symptoms resembling intestinal obstruction. These symptoms usually resolve in 3 to 5 days. HAE episodes may be related to local tissue trauma in a high percentage of cases, with dental work often regarded as the classic precipitating factor. The response to epinephrine is a useful differential point: HAE lesions do not respond well to epinephrine.

If HAE is strongly suspected, the diagnosis can be proven by appropriate measurement of complement factors (decreased levels of C1 esterase inhibitor [quantitative and functional] and C4 [also C2, during an episode of swelling]).

Treatment of C1 esterase inhibitor dysfunction includes plasma-derived C1 esterase inhibitor given intravenously and the bradykinin antagonists: ecallantide, which is a kallikrein inhibitor, and icatibant, which is a bradykinin receptor antagonist.

Physical Urticaria

Heat, light, cold, vibration, and trauma or pressure can cause hives in susceptible persons. Obtaining an accurate history is the only way of suspecting the diagnosis, which can be confirmed by applying each of the stimuli to the patient's skin. Heat can be applied by placing coins soaked in hot water for a few minutes on the patient's forearm. Cold can be applied with coins kept in a freezer or with ice cubes. For vibration, a laboratory vortex mixer or any common vibrator can be used. A pair of sandbags connected by a strap can be draped over the patient to create enough pressure to cause symptoms in those with delayed pressure urticaria. Unlike most cases of common idiopathic urticaria, in which the lesions affect essentially all skin surfaces, many cases of physical urticaria seem to involve only certain areas of skin. Thus, results of challenges will be positive only in the areas usually involved and will be negative in other areas.

Food Allergy in Chronic Urticaria

Food allergy almost never causes chronic urticaria. However, urticaria (or angioedema or anaphylaxis) can be an acute manifestation of true food allergy.

Histopathologic Features of Chronic Urticaria

Chronic urticaria is characterized by mononuclear cell perivascular cuffing around dermal capillaries, particularly involving the capillary loops that interdigitate with the rete pegs of the epidermis. Urticarial vasculitis shows the usual histologic features of leukocytoclastic vasculitis.

Management of Urticaria

The patient history is of utmost importance for discovering the 2% to 10% of cases of chronic urticaria due to secondary causes. A complete physical examination is needed, with particular attention paid to the skin (including testing for dermatographism) to evaluate for the vasculitic nature of the lesions and to the liver, lymph nodes, and mucous membranes. Laboratory testing need not be exhaustive but may include the following: chest radiography, a complete blood cell count with differential count (to discover eosinophilia), measurement of liver enzymes, tests for thyroid function and antibodies, erythrocyte sedimentation rate, serum protein electrophoresis (in patients older than 50 years), urinalysis, and stool examination for parasites. Allergy skin testing is indicated only if the patient has an element in the history suggestive of an allergic cause. However, patients with idiopathic urticaria often have fixed ideas about an allergy causing their problem, and skin testing often helps to dissuade them of this idea.

Management of urticaria and angioedema consists of blocking histamine, beginning usually with nonsedating H_1 antagonists. The addition of leukotriene antagonists may be helpful. The role of H_2 antagonists is unclear; they may help a small percentage of patients. Doxepin, a tricyclic antidepressant, has potent antihistamine effects and is useful. Omalizumab, a monoclonal antibody that blocks IgE, has received US Food and Drug Administration approval for antihistamine treatment–resistant chronic urticaria. Systemic corticosteroids can be administered for acute urticaria and angioedema.

Anaphylaxis

There is no universally accepted clinical definition of *anaphylaxis*. The manifestations of anaphylaxis vary depending on the severity and can include any combination of urticaria, angioedema, flushing, pruritus, upper-airway obstruction, lower-airway obstruction, diarrhea, nausea, vomiting, syncope, hypotension, tachycardia, and dizziness. Approximately 90% of anaphylactic episodes include urticaria or angioedema. A cellular and molecular definition of anaphylaxis is a generalized allergic reaction characterized by activated basophils and mast cells releasing many mediators (preformed and newly synthesized). The dominant mediators of acute anaphylaxis are histamine and prostaglandin D_2. The serum levels of tryptase peak at 1 hour after the onset of anaphylaxis and may stay elevated for 5 hours. Physiologically, the hypotension of anaphylaxis is caused by peripheral vasodilatation and not by impaired cardiac contractility. Anaphylaxis is characterized by a hyperdynamic state. For these reasons, anaphylaxis can be fatal in patients

Box 1.5 • Most Common Causes of Anaphylaxis

Foods (peanuts, tree nuts, fish, and shellfish)
Medications (antibiotics, neuromuscular blockers, and anticonvulsants)
Insect stings (bee, fire ant, and vespid)
Latex
Aspirin and other nonsteroidal anti-inflammatory agents

with preexisting fixed vascular obstructive disease in whom a decrease in perfusion pressure leads to a critical reduction in flow (stroke) or patients in whom laryngeal edema develops and completely occludes the airway.

The most common causes of anaphylaxis are listed in Box 1.5. Most anaphylactic events occur within 1 hour, often within minutes, after exposure to the offending agent.

Food Allergy

Clinical History

The clinical syndrome of food allergy may include the following. Persons with high levels of sensitivity have tingling, itching, and a metallic taste in the mouth while the food is still in the mouth. Within 15 minutes after the food is swallowed, epigastric distress may occur. There may be nausea and, rarely, vomiting. The person feels abdominal cramping chiefly in the periumbilical area (small-bowel phase), and lower abdominal cramping and watery diarrhea may occur. Urticaria or angioedema may occur in any distribution, or there may be only itching of the palms and soles. With increasing clinical sensitivity to the offending allergen, anaphylactic symptoms may emerge, including tachycardia, hypotension, generalized flushing, and alterations of consciousness.

In extremely sensitive persons, generalized flushing, hypotension, and tachycardia may occur before the other symptoms. Most patients with a food allergy can identify the offending foods. The diagnosis should be confirmed by skin testing or in vitro measurement of allergen-specific IgE antibody. Items considered to be the most common causes of food allergy are listed in Box 1.6.

Box 1.6 • Common Causes of Food Allergy

Eggs
Milk
Nuts
Peanuts
Shellfish
Soybeans
Wheat

Food-Related Anaphylaxis

Food-induced anaphylaxis is the same process as acute urticaria or angioedema induced by food allergens, except that the reaction is more severe in anaphylaxis. Relatively few foods are commonly involved in food-induced anaphylaxis; the main ones are peanuts, shellfish, and nuts. Yet, any food has the potential to cause anaphylaxis. In patients with latex allergy, food allergy can develop to banana, avocado, kiwifruit, and other fruits.

KEY FACTS

✓ Hereditary angioedema—recurrent angioedema, typically without urticaria

✓ Heat, light, cold, vibration, and trauma or pressure—can cause physical urticaria

✓ Urticaria and angioedema—are managed by blocking histamine

✓ Food-induced anaphylaxis—same process but more severe reaction than acute food-induced urticaria or angioedema

Allergy Skin Testing in Food Allergy

Patients presenting with food-related symptoms may have food allergy, food intolerance, irritable bowel syndrome, nonspecific dyspepsia, or a nonallergic condition. A careful and detailed history on the nature of the “reaction,” the reproducibility of the association of food and symptoms, and the timing of symptoms in relation to the ingestion of food can help the clinician form a clinical impression.

In many cases, allergy skin tests to foods can be helpful. If the results are negative (and the clinical suspicion for food allergy is low), the patient can be reassured that food allergy is not the cause of the symptoms. If the results are positive (and the clinical suspicion for food allergy is high), the patient should be counseled about management of the food allergy. The patient should strictly avoid the food and possible cross-reactive foods. These patients should also be given an epinephrine kit for self-administration in an emergency. Although some food allergies may be outgrown, peanut, tree nut, fish, and shellfish allergies are typically lifelong.

If the diagnosis of food allergy is uncertain or the symptoms are mild and nonspecific, oral food challenges may be helpful. An open challenge is usually performed first. If the results are negative, the diagnosis of food allergy is excluded. If the results are positive but there is suspicion about the results, a blinded placebo-controlled challenge test can be performed.

Stinging Insect Allergy

In patients clinically sensitive to Hymenoptera, reactions to a sting can be either large local reactions or systemic, anaphylactic reactions. With a large local sting reaction, swelling at the sting site may be dramatic, but there are no symptoms distant from that site. Stings of the head, neck, and dorsum of the hands are particularly prone to large local reactions.

Anaphylaxis caused by allergy to stinging insects is similar to all other forms of anaphylaxis. Thus, the onset of anaphylaxis may be very rapid, often within 1 or 2 minutes. Pruritus of the palms and soles is the most common initial manifestation. Frequently, 1 or more of the following occur next: generalized flushing, urticaria, angioedema, or hypotension. The reason for attaching importance to whether a stinging insect reaction is a large local one or a generalized reaction is that allergy skin testing and allergen immunotherapy are recommended only for generalized reactions. Patients who have a large local reaction are not at significantly increased risk for future anaphylaxis.

Bee and Vespid Allergy

Yellow jackets, wasps, and hornets are vespids, and their venoms cross-react to a substantial degree. The venom of honeybees (family, Apidae) does not cross-react with that of vespids. Thus, it usually is appropriate to conduct skin testing for allergy to honeybee and to each of the vespids. In most cases, patients will not be able to identify the causative stinging insect.

Allergy Testing

Patients who have had a generalized reaction need allergen skin testing. Patients who have had a large local reaction to a Hymenoptera sting do not need allergen skin testing because they are not at significantly increased risk for future anaphylaxis.

In many cases, skin testing should be delayed for at least 1 month after a sting-induced generalized reaction, because tests conducted closer to the time of the sting have a substantial risk of false-negative results. Positive results that correlate with the clinical history are sufficient evidence for considering Hymenoptera venom immunotherapy.

Venom Immunotherapy

General indications for venom immunotherapy are listed in Box 1.7. Patients must understand that after immunotherapy is begun, the injection schedule must be maintained and that immunotherapy itself has a small risk of allergic reaction. Patients also need to understand that despite receiving allergy immunotherapy, they must carry epinephrine when outdoors because of the possibility (from 2% with vespid stings to 10% with apid stings) that immunotherapy will not provide suitable protection. Most, but not all, patients can safely discontinue venom immunotherapy after 5 years of treatment.

Box 1.7 • Indications for Insect Venom Immunotherapy

History of mild, moderate, or severe anaphylaxis to a sting

Positive results on skin tests to the venom that was implicated historically in the anaphylactic reaction

Urticaria distant from the site of the sting (adults only)

Box 1.8 • Dos and Don’ts for Patients With Hypersensitivity to Insect Stings

Avoid looking or smelling like a flower

Avoid wearing flowered-print clothing

Avoid using cosmetics and fragrances, especially ones derived from flowering plants

Never drink from a soft-drink can outdoors during the warm months—a yellow jacket can land *on* or *in* the can while you are not watching, go inside the can, and sting the inside of your mouth (a dangerous place for a sensitive patient to be stung) when you take a drink

Never reach into a mailbox without first looking inside it

Never go barefoot

Always look at the underside of picnic table benches and park benches before sitting down

Avoidance

The warnings that every patient with stinging insect hypersensitivity should receive are listed in Box 1.8. A patient’s specific circumstances may require additions to this list. Also, patients need to know how to use self-injectable epinephrine. Many patients wear an anaphylaxis identification bracelet.

Drug Allergy

Drug Allergy Not Involving IgE or Immediate-Type Reactions

Patients with drug allergy not involving IgE or immediate-type reactions have negative results on skin prick and intradermal testing.

Stevens-Johnson Syndrome

Stevens-Johnson syndrome is a bullous skin and mucosal reaction; very large blisters appear over much of the skin surface, in the mouth, and along the gastrointestinal tract. Because of the propensity of the blisters to break down and become infected, the reaction often is life-threatening. Treatment consists of stopping use of the drug that causes the reaction, giving corticosteroids systemically, and providing supportive care. The patients are often treated in burn units. Penicillin, sulfonamides, barbiturates, diphenylhydantoin, warfarin, and phenothiazines are well-known causes. A drug-induced Stevens-Johnson reaction is an absolute contraindication to administering the causative drug to the patient in the future. The mortality rate is approximately 5% to 10%.

Toxic Epidermal Necrolysis

Clinically, toxic epidermal necrolysis is almost indistinguishable from Stevens-Johnson syndrome. In general, Stevens-Johnson syndrome involves 10% or less of the skin and toxic epidermal necrolysis involves more than 30%. Histologically, the cleavage plane for the blisters is deeper than in Stevens-Johnson syndrome. The cleavage plane is at the basement membrane of the epidermis, so even the basal cell layer is lost. This makes toxic epidermal necrolysis even more devastating than Stevens-Johnson syndrome because healing occurs with much scarring. Often, healing cannot be accomplished without skin grafting, so the mortality rate can be as high as 90% in more severe cases. Patients with toxic epidermal necrolysis should always be cared for in a burn unit because of full-thickness damage over 80% to 90% of the skin.

KEY FACTS

- ✓ Venoms—of vespids (eg, yellow jackets, wasps, hornets) cross-react; of vespid and honeybee do not cross-react
- ✓ Patients with stinging insect allergy—need to know how to use self-injectable epinephrine
- ✓ Stevens-Johnson syndrome—very large blisters on the skin, in the mouth, and along the gastrointestinal tract
- ✓ Toxic epidermal necrolysis and Stevens-Johnson syndrome—are almost indistinguishable clinically

Morbilliform Skin Reaction

Morbilliform skin reaction is the most common dermatologic manifestation of a drug reaction. It is an immune-mediated drug rash without IgE involvement, manifested by a macular-papular exanthem. The rash can be accompanied by pruritus but has no other systemic symptoms. It typically occurs more than 5 days after the use of a medication was begun. Morbilliform skin reaction is not associated with anaphylaxis or other serious sequelae.

Ampicillin-Mononucleosis Rash

Ampicillin-mononucleosis rash is a distinctive drug rash that occurs when ampicillin is given to an acutely ill, febrile patient who has mononucleosis. The rash is papular, nonpruritic, and rose colored. It occurs usually on the abdomen and feels granular when fingers brush lightly over the surface of the involved skin. It is not known why the rash is specific for ampicillin and mononucleosis. This rash does not predispose to allergy to penicillin.

Key Definition

Ampicillin-mononucleosis rash: *unique drug rash that occurs when ampicillin is given to an acutely ill, febrile patient who has mononucleosis.*

Fixed Drug Eruptions

Fixed drug eruptions are red to red-brown macules that appear on a certain area of the patient's skin; any part of the body can be affected. The macules do not itch or have other signs of inflammation, although fever is associated with their appearance in a few patients. The unique aspect of this phenomenon is that if a patient is given the same drug in the future, the rash develops in exactly the same skin areas. Resolution of the macules often includes postinflammatory hyperpigmentation. Except for cosmetic problems due to skin discoloration, the phenomenon does not seem serious. Antibiotics and sulfonamides are the most frequently recognized causes.

Erythema Nodosum

Erythema nodosum is a characteristic rash of red nodules about the size of a quarter, usually nonpruritic and appearing only over the anterior aspects of the lower legs. Histopathologically, the nodules are plaques of infiltrating mononuclear cells. Erythema nodosum is associated with several connective tissue diseases, viral infections, and drug allergy.

Contact Dermatitis

Contact dermatitis can occur with various drugs. Commonly, it is a form of drug allergy that is an occupational disease in medical or health care workers. In some patients receiving topical drugs, allergy develops to the drug or to various elements in its pharmaceutical formulation (eg, fillers, stabilizers, antibacterials, emulsifiers). Contact dermatitis is a manifestation of type IV hypersensitivity. Clinically, it appears as an area of reddening on the skin that progresses to a granular, weeping eczematous eruption with some dermal thickening; the surrounding skin has a plaquelike quality.

When patients are receiving treatment for dermatitis and contact hypersensitivity develops to corticosteroids or other drugs used in the treatment, a particularly difficult diagnostic problem arises unless the physician is alert to this possibility. When contact hypersensitivity to a drug occurs, it does not increase the probability of acute type I hypersensitivity and is not associated with serious exfoliative syndromes. However, exquisite cutaneous sensitivity of this type can develop to a degree that almost no avoidance technique in the workplace completely eliminates dermatitis; even protective gloves are only partly helpful. Thus, it can be occupationally disabling.

Drug Allergy Involving IgE or Immediate-Type Reactions

Penicillin Allergy

Penicillin can cause anaphylaxis in sensitive persons. Penicillin allergy is an IgE-mediated process that can be evaluated with skin testing to the major and minor determinants of penicillin.

Penicillin skin tests can be helpful in determining whether it is safe to administer penicillin to a patient with suspected penicillin allergy. About 85% of patients who give a history of penicillin allergy have negative results of skin tests to the major and minor determinants of penicillin. These patients are not at increased risk for anaphylaxis and can receive penicillin safely. If penicillin skin test results are positive, there is a 40% to 60% chance that an allergic reaction will develop if the patient is challenged with penicillin. These patients should avoid penicillin and related drugs. However, if there is a strong indication for penicillin treatment, desensitization can be performed. The desensitization procedure involves administration of progressively increasing doses of penicillin. Desensitization can be accomplished by the oral or intravenous route and is usually performed in a hospital setting.

Ampicillin, amoxicillin, nafcillin, and other β-lactam antibiotics cross-react strongly with penicillin. Early studies suggested that up to 30% of patients with penicillin allergy were also allergic to cephalosporins. More recent studies have suggested that the cross-sensitivity of penicillin with cephalosporins is much less (about 5%). Most studies have suggested that aztreonam does not cross-react with penicillin.

Radiocontrast Media Reactions

Radiocontrast media can cause reactions that have the clinical appearance of anaphylaxis. Estimates of the frequency of these reactions are 2% to 6% of procedures involving intravenous contrast media. The prevalence of intra-arterial contrast-induced reactions is lower. Anaphylactoid reactions do not involve IgE antibody (thus the term *anaphylactoid*). Radiocontrast media appear to induce mediator release on the basis of some other property intrinsic to the contrast agent. The tonicity or ionic strength of the medium seems particularly related to anaphylactoid reactions. Since nonionic and low-osmolar media became available, the incidence of reactions has decreased.

The frequency of radiocontrast media reactions can be reduced with the use of nonionic or low-osmolar media for patients with a history of asthma or atopy. Patients who have a history of reaction to radiocontrast media and who subsequently need procedures that use radiocontrast media can be pretreated with a protocol of prednisone, 50 mg orally every 6 hours for 3 doses, with the last dose given 1 hour before the procedure. At the last dose, addition of 50 mg of diphenhydramine or an equivalent H_1 antagonist is recommended. Some studies show that the addition of oral ephedrine can be beneficial. Most studies show that the addition of an H_2 antagonist is unnecessary.

Other Allergic or Immunologic Conditions

Mastocytosis

Systemic mastocytosis is a disorder of abnormal proliferation of mast cells. The skin, bone marrow, liver, spleen, lymph nodes, and gastrointestinal tract can be affected. The clinical manifestations vary but can include flushing, pruritus, urticaria, unexplained syncope, fatigue, and dyspepsia. Bone marrow biopsies with stains for mast cells (toluidine blue, Giemsa, or chloral acetate esterase) and immunochemical stains for tryptase are the most direct diagnostic studies. Serum levels of tryptase and urinary concentrations of histamine, histamine metabolites, and prostaglandins are typically increased.

Treatment initially consists of antihistamines. Cromolyn sodium given orally can be beneficial, especially in patients with gastrointestinal tract symptoms. Corticosteroids should be considered in severe cases, and interferon is a promising investigational treatment.

Eosinophilia

Eosinophilia is idiopathic, primary, or secondary (reactive). Hypereosinophilia syndrome is an idiopathic eosinophilic disorder characterized by an absolute eosinophil count of more than 1.5×10^9/L; a course of 6 months or longer; organ involvement as manifested by eosinophilia-mediated tissue injury (cardiomyopathy, dermatitis, pneumonitis, sinusitis, gastrointestinal tract inflammation, left or right ventricular apical thrombus, or stroke); and no other causes of eosinophilia. The syndrome typically affects persons in the third through sixth decades of life, and women are affected more often than men. Symptoms include fatigue, cough, shortness of breath, or rash. Cardiac involvement in hypereosinophilia syndrome is especially significant: Endomyocardial fibrosis, mural thrombi, and mitral and tricuspid incompetence can occur. The clinical syndrome is manifested as restrictive cardiomyopathy with congestive heart failure. Echocardiography and endomyocardial biopsy are important diagnostic tests.

Secondary causes include the following: infections (tissue-invasive parasitosis); drugs; toxins; inflammation; atopy and allergies (asthma); malignancy (lymphoma, Hodgkin lymphoma, cutaneous T-cell lymphoma, and metastatic cancer); collagen vascular disease (eosinophilic vasculitis); pulmonary disease (hypereosinophilic pneumonitis and Löffler syndrome); and eosinophilic myalgia syndrome.

The clinical diagnostic approach is to exclude secondary eosinophilic disorders, to evaluate bone marrow aspirates and biopsy specimens with genetic and molecular studies, and to perform tests to assess eosinophilia-mediated tissue injury (chest radiography, pulmonary function tests, echocardiography, complete blood cell count, and liver enzyme and serum tryptase levels). The differential diagnosis of eosinophilia is given in Box 1.9.

Hypereosinophilia syndrome is treated with prednisone, 1 mg/kg daily, alone or in combination with hydroxyurea. Second-line therapy includes recombinant interferon-alfa.

Primary Humoral Immunodeficiency

Most primary immunodeficiencies are diagnosed during childhood. The most common immunodeficiencies diagnosed in adults are IgE deficiency and common variable immunodeficiency (CVID). Selective immunoglobulin A (IgA) deficiency occurs in approximately 0.5% of the US population, with the majority being asymptomatic. If the IgA level is

Box 1.9 • Common Causes of Eosinophilia

Typically mild eosinophilia (eosinophil count, 0.5-1.0×10^9/L)
- Atopic
- Allergic bronchopulmonary aspergillosis
- Asthma
- Atopic dermatitis
- Drug hypersensitivity (sometimes very high eosinophil levels)
- Vasculitis/connective tissue disease

Typically moderate to severe eosinophilia (eosinophil count, >1.0×10^9/L)
- Proliferative/neoplastic
- Idiopathic hypereosinophilic syndrome
- Churg-Strauss vasculitis
- Eosinophilic fasciitis
- Eosinophilic gastroenteritis
- Helminth infection
- Eosinophilia-myalgia syndrome

very low, at less than 7.0 mg/dL, then the patient may be at risk for a transfusion reaction because of the presence of anti-IgA antibodies. IgA-depleted products should be used for transfusions.

CVID affects male and female persons of all ages. Patients have recurrent pyogenic infections with encapsulated organisms and conditions that include chronic otitis media, chronic or recurrent sinusitis, pneumonia, and bronchiectasis. The primary laboratory abnormality is hypogammaglobulinemia (low immunoglobulin G levels). Typically, IgA or immunoglobulin M levels are also decreased.

KEY FACTS

- ✓ Penicillin—can cause anaphylaxis in sensitive persons; evaluate with skin testing
- ✓ Patients with a history of penicillin allergy—about 85% have negative skin test results
- ✓ Radiocontrast media reactions—estimated frequency is 2% to 6% of procedures
- ✓ Mastocytosis—clinical manifestations vary; bone marrow biopsy and staining are most direct diagnostic studies
- ✓ CVID—affects both sexes and all ages; most common primary immunodeficiency in adults

Patients with CVID often have autoimmune or gastrointestinal tract disturbances. About one-half of patients have chronic diarrhea and malabsorption. They may have steatorrhea, protein-losing enteropathy, ulcerative colitis, or Crohn disease. Other gastrointestinal tract problems associated with the disease are atrophic gastritis, pernicious anemia, giardiasis, and chronic active hepatitis. Pathologic changes in the gastrointestinal tract mucosa include loss of villi, nodular lymphoid hyperplasia, and diffuse lymphoid infiltration.

Autoimmune anemia, thrombocytopenia, or neutropenia is present in 10% to 50% of CVID patients and can occur before CVID diagnosis. Inflammatory arthritis and lymphoid interstitial pneumonia are other associated conditions. In addition, patients have increased risk of a malignancy, particularly a lymphoid malignancy such as non-Hodgkin lymphoma.

The diagnosis of CVID should be considered if patients have recurrent pyogenic infections and hypogammaglobulinemia. Associated gastrointestinal tract or autoimmune disease and the exclusion of hereditary primary immunodeficiencies support the diagnosis. Treatment is with monthly intravenous or weekly subcutaneous γ-globulin. The typical total dosage is 400 to 600 mg/kg monthly.

Terminal Complement Component Deficiencies

Patients with deficiency of the terminal complement component C5, C6, C7, or C8 have an increased susceptibility to meningococcal infections.

Terminal complement component deficiency should be suspected if patients have recurrent meningococcal disease, a family history of meningococcal disease, systemic meningococcal infection, or infection with an unusual serotype of meningococcus. Diagnosis is confirmed with assay of total hemolytic complement and measurement of individual complement components.

2

Asthma[a]

GERALD W. VOLCHECK, MD

Asthma is a common disease affecting approximately 8% of the adult population. This chapter focuses on categorizing asthma, identifying contributors to asthma, and reporting asthma medical management based on severity.

Presentation and Diagnosis

Medical History

A medical history for asthma includes careful inquiry about symptoms, provoking factors, alleviating factors, and severity. The hallmark symptoms for asthma are wheeze, cough, and shortness of breath. Patients with marked respiratory allergy have symptoms when exposed to aeroallergens and often have seasonal variation of symptoms. If allergy skin patch test results are negative, one can be reasonably certain that the patient does not have allergic asthma, but rather intrinsic or nonallergic asthma. Respiratory infections (particularly viral); cold dry air; exercise; and respiratory irritants can trigger allergic and nonallergic asthma.

Methacholine Bronchial Challenge

If a patient has a history suggestive of episodic asthma but has normal results on pulmonary function tests on the day of the examination, the patient is a reasonable candidate for a methacholine bronchial challenge. The methacholine bronchial challenge is also useful in evaluating patients for cough when baseline pulmonary function appears normal. Positive results indicate that bronchial hyperresponsiveness is present, although results can be positive in conditions besides asthma (Box 2.1). Some allergists consider isocapnic hyperventilation with subfreezing dry air (by either exercising or breathing a carbon dioxide–air mixture) or exercise testing as alternatives to a methacholine challenge.

A methacholine challenge should not be performed for patients who have severe airway obstruction or a clear diagnosis of asthma. Usually, a 20% decrease in forced expiratory volume in 1 second (FEV_1) is considered a positive result.

Exhaled Nitric Oxide

Exhaled nitric oxide has been studied as a noninvasive measure of airway inflammation. The fraction of nitric oxide in the exhaled air increases in proportion to inflammation of the bronchial wall, sputum eosinophilia, and airway hyperresponsiveness. Exhaled nitric oxide levels increase with deterioration in asthma control and decrease in a dose-dependent manner with anti-inflammatory treatment. The usefulness of measuring exhaled nitric oxide may be in monitoring asthma control, guiding therapy, and predicting response to corticosteroid therapy.

Pathophysiology

Bronchial hyperresponsiveness and airway inflammation are common to all forms of asthma. Hyperresponsiveness is measured by assessing pulmonary function before and after exposure to albuterol, methacholine, histamine, cold air, or exercise. A decrease in FEV_1 of 20% or more with challenge or an increase in FEV_1 of 12% or more with albuterol is considered a sign of airway hyperreactivity.

Persons who have allergic asthma generate mast cell and basophil mediators. These mediators have important roles in

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[a] Portions previously published in Volcheck GW. Clinical allergy: diagnosis and management. Totowa (NJ): Humana Press; c2009; used with permission of Mayo Foundation for Medical Education and Research.

Box 2.1 • Conditions Associated With Positive Findings on Methacholine Challenge

- Current asthma
- Past history of asthma
- Chronic obstructive pulmonary disease
- Smoking
- Recent respiratory infection
- Chronic cough
- Allergic rhinitis

the development of endobronchial inflammation and smooth muscle changes that occur after acute exposure to allergen. Mast cells and basophils are prominent during the immediate-phase reaction. In the late-phase reaction to allergen exposure, the bronchi show histologic features of chronic inflammation and eosinophils become prominent in the reaction.

Patients who have chronic asthma and negative results on allergy skin tests usually have an inflammatory infiltrate in the bronchi and histologic findings dominated by eosinophils when asthma is active. Patients with sudden asphyxic asthma may have a neutrophilic rather than an eosinophilic infiltration of the airway. The pathologic features of asthma have been studied chiefly in fatal cases; some bronchoscopic data are available for mild and moderate asthma. The histologic hallmarks of asthma include mucous gland hypertrophy, mucus hypersecretion, epithelial desquamation, widening of the basement membrane, and infiltration by eosinophils (Box 2.2).

Important characteristics of cytokines are summarized in Table 2.1. Interleukin (IL)-1, IL-6, and tumor necrosis factor are produced by antigen-presenting cells and start the acute inflammatory reaction; IL-4 and IL-13 stimulate immunoglobulin (Ig) E synthesis; IL-5 stimulates eosinophils; IL-2 and interferon-γ stimulate a cell-mediated response; and IL-10 is the primary anti-inflammatory cytokine.

Box 2.2 • Histologic Hallmarks of Asthma

- Mucous gland hypertrophy
- Mucus hypersecretion
- Alteration of tinctorial and viscoelastic properties of mucus
- Widening of basement membrane zone of bronchial epithelial membrane
- Increased number of intraepithelial leukocytes and mast cells
- Round cell infiltration of bronchial submucosa
- Intense eosinophilic infiltration of submucosa
- Widespread damage to bronchial epithelium
  - Large areas of complete desquamation of epithelium into airway lumen
  - Mucus plugs filled with eosinophils and their products

Table 2.1 • Characteristics of Cytokines

Cytokine	Major Actions	Primary Sources
IL-1	Lymphocyte activation Fibroblast activation Fever	Macrophages Endothelial cells Lymphocytes
IL-2	T- and B-cell activation	T cells (T_H1)
IL-3	Mast cell proliferation Neutrophil and macrophage maturation	T cells Mast cells
IL-4	IgE synthesis	T cells (T_H2)
IL-5	Eosinophil proliferation and differentiation	T cells (T_H2)
IL-6	IgG synthesis Lymphocyte activation	Fibroblasts T cells
IL-8	Neutrophil chemotaxis	Fibroblasts Endothelial cells Monocytes
IL-10	Inhibition of IFN-γ and IL-1 production	T cells Macrophages
IL-13	IgE synthesis	T cells
IFN-α	Antiviral activity	Leukocytes
IFN-γ	Macrophage activation Stimulation of MHC expression Inhibition of T_H2 activity	T cells (T_H1)
TNF-γ	Antitumor cell activity	Lymphocytes Macrophages
TNF-β	Antitumor cell activity	T cells
GM-CSF	Mast cell, granulocyte, and macrophage stimulation	Lymphocytes Mast cells Macrophages

Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IgE, immunoglobulin E; IgG, immunoglobulin G; IL, interleukin; MHC, major histocompatibility complex; T_H, helper T cell; TNF, tumor necrosis factor.

Differential Diagnosis

The differential diagnosis of wheezing is given in Box 2.3.

Assessment of Severity

Asthma is **intermittent** if 1) daytime symptoms are intermittent (≤2 times weekly), 2) continuous treatment is not needed, and 3) the flow-volume curve during formal pulmonary function testing is normal between episodes of symptoms (Table 2.2). Even for patients who meet these criteria, inflammation (albeit patchy) is present in the airways and corticosteroid inhaled on a regular basis diminishes bronchial hyperresponsiveness.

Box 2.3 • Differential Diagnosis of Wheezing

- Pulmonary embolism
- Cardiac failure
- Foreign body
- Central airway tumors
- Aspiration
- Carcinoid syndrome
- Chondromalacia or polychondritis
- Löffler syndrome
- Bronchiectasis
- Tropical eosinophilia
- Hyperventilation syndrome
- Laryngeal edema
- Vascular ring affecting trachea
- Factitious
- α_1-Antitrypsin deficiency
- Immotile cilia syndrome
- Bronchopulmonary dysplasia
- Bronchiolitis (including bronchiolitis obliterans), croup
- Cystic fibrosis
- Vocal cord dysfunction

Asthma is **mild persistent** or **moderate persistent** when 1) the symptoms occur with regularity (>2 times weekly) or daily, 2) there is nocturnal occurrence of symptoms, or 3) asthma exacerbations are troublesome. For many of these patients, the flow-volume curve is rarely normal and complete pulmonary function testing may show evidence of hyperinflation, as indicated by increased residual volume or an increase above expected levels for the diffusing capacity of the lung for carbon dioxide. Asthma is **severe persistent** when symptoms are present almost continuously and the usual medications must be given in doses at the upper end of the dose range to control the disease.

Key Definition

Intermittent asthma: *the daytime symptoms are intermittent (<2 times weekly), continuous treatment is not needed, and flow-volume curve during pulmonary function testing is normal between episodes.*

Key Definition

Mild persistent *or* **moderate persistent asthma:** *symptoms occur with some regularity (>2 times weekly) or daily, symptoms occur at night, or exacerbations are troublesome.*

Patients with mild, moderate, or severe persistent asthma should receive treatment daily with anti-inflammatory medications, usually inhaled corticosteroids (Figure 2.1). Most patients with severe asthma require either large doses of inhaled corticosteroid or oral prednisone daily for adequate control (Table 2.3). A majority of patients have been hospitalized more than once for asthma. The severity of asthma can change over time, and an early sign that asthma is not well controlled is the emergence of nocturnal symptoms.

Conditions Contributing to Asthma

Assessment of Contributors to Asthma

The mnemonic *AIR-SMOG* provides a concise checklist of possible contributors to asthma (Box 2.4). In addition, patient adherence to therapy and ability to use the inhaler correctly should be reviewed at least annually for all patients with persistent asthma.

Upper Airway Cough Syndrome

Upper airway cough syndrome should be separated from asthma. This condition manifests primarily as chronic cough and does not include wheeze or shortness of breath. The cough is precipitated by postnasal drainage. Etiologic factors for this condition include allergic and nonallergic rhinitis and chronic sinusitis. Treatment is geared toward the underlying cause.

Gastroesophageal Reflux and Asthma

The precise role of gastroesophageal reflux in asthma is not known. There appears to be a subgroup of patients whose asthma is exacerbated by gastroesophageal reflux.

Asthma-Provoking Drugs

It is important to recognize the potentially severe adverse response that patients with asthma may show to β_1- and β_2-blockers, including β_1-selective blockers such as atenolol. Patients with asthma who have glaucoma treated with ophthalmic preparations of timolol or betaxolol may have bronchospasm. β-Blockers are not absolutely contraindicated in asthma, but observation is warranted.

Table 2.2 • Levels of Asthma Severity as Classified by the National Asthma Education and Prevention Program

	Classifications of Asthma Severity,[b] Patients Age ≥12 y			
		Persistent		
Components of Severity[a]	**Intermittent**	**Mild**	**Moderate**	**Severe**
Symptoms	≤2 d/wk	>2 d/wk but not daily	Daily	Throughout the day
Nighttime awakenings	≤2 times/mo	3-4 times/mo	>1 time/wk but not nightly	Often 7 times/wk
Short-acting β_2-agonist use for symptom control	≤2 d/wk	>2 d/wk but not >1 time/d	Daily	Several times per day
Interference with normal activity	None	Minor limitation	Some limitation	Extreme limitation
Lung function	Normal FEV_1 between exacerbations FEV_1 >80% predicted FEV_1/FVC normal	FEV_1 ≥80% predicted FEV_1/FVC normal	FEV_1 >60% but <80% predicted FEV_1/FVC reduced 5%	FEV_1 ≥20% FEV_1/FVC reduced >5%
Risk[c]				
Exacerbations[d] requiring oral systemic corticosteroids	0-1/y Consideration[e]	≥2/y Consideration[e]	≥2/y Consideration[e]	≥2/y Consideration[e]

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

[a] Impairment with normal FEV_1/FVC: 8-19 y of age (yoa), 85%; 20-39 yoa, 80%; 40-59 yoa, 75%; 60-80 yoa, 70%.

[b] Severity level is determined with assessment of both impairment and risk. The impairment domain is assessed by the patient's or caregiver's recall of previous 2-4 wk and spirometry. Severity is assigned to the most severe category in which any feature occurs.

[c] Relative annual risk of exacerbations may be related to FEV_1.

[d] Data are inadequate to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (requiring urgent unscheduled care, hospitalization, intensive care unit admission) indicate greater underlying disease severity. For treatment purposes, patients who have ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

[e] Consideration of severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.

Modified from National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. [cited 2018 Mar 12.] Bethesda (MD): National Heart, Lung, and Blood Institute; 2007. p 43. Available from: nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.

KEY FACTS

- ✓ A decrease in FEV_1 ≥20% with challenge—sign of airway hyperreactivity
- ✓ Hallmark symptoms for asthma—wheeze, cough, and shortness of breath
- ✓ Methacholine bronchial challenge—its consideration is recommended if the patient's history suggests episodic asthma but results of pulmonary function tests are normal on examination day
- ✓ Exhaled nitric oxide—useful in monitoring asthma control, guiding therapy, and predicting response to corticosteroids
- ✓ β-Blockers—not absolutely contraindicated in asthma, but observation is warranted

A chronic dry cough that mimics asthma may develop in persons taking angiotensin-converting enzyme inhibitor drugs. Wheeze and dyspnea, however, do not accompany the cough.

Aspirin ingestion can cause acute, severe, and fatal asthma in a small subset of patients with asthma. Most of the affected patients have nasal polyposis, hyperplastic pansinus mucosal disease, and moderate to severe persistent asthma. However, not all patients with this reaction to aspirin fit the profile. Many nonsteroidal anti-inflammatory drugs can trigger the reaction; the likelihood correlates with a drug's potency for inhibiting cyclooxygenase. Only nonacetylated salicylates such as choline salicylate (a weak cyclooxygenase inhibitor) seem not to provoke the reaction. Leukotriene-modifying drugs may be particularly helpful in aspirin-sensitive asthma.

Traditionally, patients with asthma have been warned not to take antihistamines because the anticholinergic activity of some antihistamines was thought to cause drying of lower respiratory tract secretions, further worsening the asthma. However, antihistamines do not worsen asthma, and some studies have shown a beneficial effect.

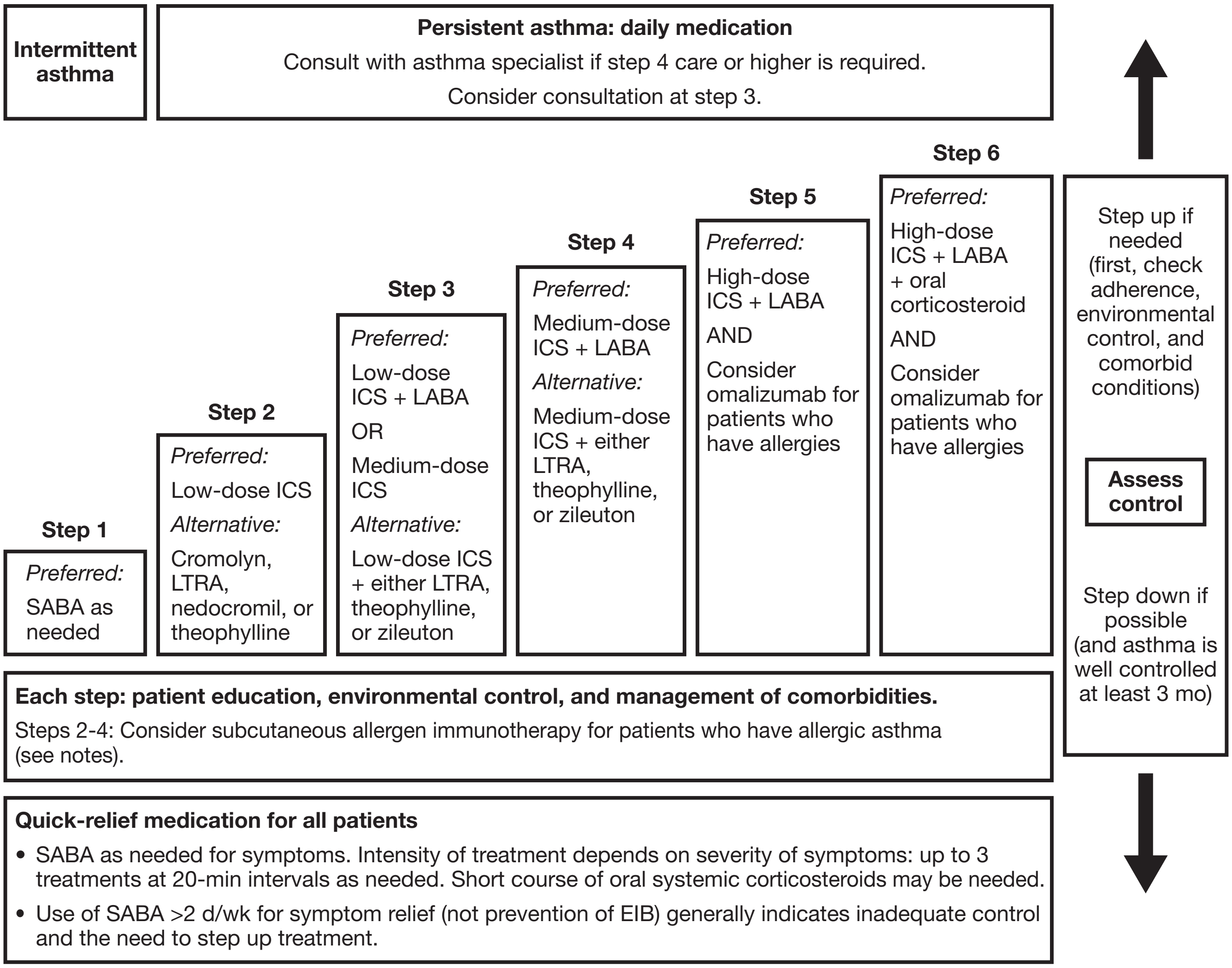
Intermittent asthma
Persistent asthma: daily medication
Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.
Step 1
Preferred:
SABA as needed
Step 2
Preferred:
Low-dose ICS
Alternative:
Cromolyn, LTRA, nedocromil, or theophylline
Step 3
Preferred:
Low-dose ICS + LABA
OR
Medium-dose ICS
Alternative:
Low-dose ICS + either LTRA, theophylline, or zileuton
Step 4
Preferred:
Medium-dose ICS + LABA
Alternative:
Medium-dose ICS + either LTRA, theophylline, or zileuton
Step 5
Preferred:
High-dose ICS + LABA
AND
Consider omalizumab for patients who have allergies
Step 6
Preferred:
High-dose ICS + LABA + oral corticosteroid
AND
Consider omalizumab for patients who have allergies
Step up if needed (first, check adherence, environmental control, and comorbid conditions)
Assess control
Step down if possible (and asthma is well controlled at least 3 mo)
Each step: patient education, environmental control, and management of comorbidities.
Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).
Quick-relief medication for all patients
• SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-min intervals as needed. Short course of oral systemic corticosteroids may be needed.
• Use of SABA >2 d/wk for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

Figure 2.1. *Stepwise Approach for Asthma Management in Children and Adults. Long-acting anticholinergic inhaler (eg, tiotropium) can be used in steps 4-6. The biologics mepolizumab, reslizumab, and benralizumab can be used in steps 5 and 6. EIB indicates exercise-induced bronchoconstriction; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β_2-agonist.*

Notes that accompany this table can be found at https://www.nhlbi.nih.gov/files/docs/guidelines/asthsumm.pdf. (Modified from National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. [cited 2018 Mar 12.] Bethesda (MD): National Heart, Lung, and Blood Institute; 2007. p. 45. Available from: nhlbi.nih.gov/guidelines/asthma/ asthgdln.htm.)

Cigarette Smoking and Asthma

The combination of asthma and cigarette smoking leads to accelerated chronic obstructive pulmonary disease. Because of the accelerated rate of irreversible obstruction, all patients with asthma who smoke should be counseled to stop smoking.

Environmental tobacco smoke is an important asthma trigger. In particular, children with asthma who are exposed to environmental smoke have more respiratory infections and asthma attacks.

Subtypes of Asthma

Asthma in Pregnancy

During pregnancy, asthma will worsen in one-third of asthmatic women, stay the same in one-third, and improve in one-third. The patient group that has worsening asthma usually has poor asthma control at the onset of pregnancy. The major risk to the mother and fetus is hypoxemia secondary to an asthma exacerbation, not the medications used to treat asthma. Generally, the pregnant asthmatic patient should be treated the same as

Table 2.3 • Stepped Asthma Treatment Based on Severity Classification of the National Asthma Education and Prevention Program

Asthma Severity Classification	Treatment[a]
Intermittent	Step 1
Persistent	
Mild	Step 2
Moderate	Step 3 or step 4
Severe	Step 5 or step 6

[a] Lowest level of treatment required to maintain symptom control.

Modified from National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. [cited 2018 Mar 12.] Bethesda (MD): National Heart, Lung, and Blood Institute; 2007. p 16. Available from: nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.

a nonpregnant asthmatic person, with the overlying guideline of using the least amount of medication required to maintain symptom stability.

Occupational Asthma

The incidence of occupational asthma is estimated to be 6% to 15% of all cases of adult-onset asthma. A large fraction of occupational asthma escapes diagnosis because physicians often obtain an inadequate occupational history. A wide range of possible industrial circumstances may lead to exposure and resultant disease. The most widely recognized causes of occupational asthma are listed in Box 2.5. Breathing tests performed in the workplace and away from the workplace aid in the diagnosis.

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis is an obstructive lung disease caused by an immunologic reaction to *Aspergillus fumigatus* in the lower airway. The typical presentation is severe corticosteroid-dependent asthma. Most patients with this condition have coexisting asthma or cystic fibrosis. The diagnostic features of allergic bronchopulmonary aspergillosis are summarized in Box 2.6. Fungi other than *A fumigatus* can cause an allergic bronchopulmonary mycosis similar to allergic bronchopulmonary aspergillosis.

Box 2.4 • AIR-SMOG: A Mnemonic for a Checklist of Contributors to Asthma

A—allergy
I—infection, irritants
R—rhinosinusitis
S—smoking
M—medications
O—occupational exposures
G—gastroesophageal reflux disease

Box 2.5 • Industrial Agents That Can Cause Asthma

- Metals
  - Salts of platinum, nickel, and chrome
- Wood dusts
  - Mahogany
  - Oak
  - Redwood
  - Western red cedar (plicatic acid)
- Vegetable dusts
  - Castor bean
  - Cotton
  - Cottonseed
  - Flour
  - Grain (mite and weevil antigens)
  - Green coffee
  - Gums
- Industrial chemicals and plastics
  - Ethylenediamine
  - Phthalic and trimellitic anhydrides
  - Polyvinyl chloride
  - Toluene diisocyanate
- Pharmaceutical agents
  - Phenylglycine acid chloride
  - Penicillins
  - Spiramycin
- Food industry agents
  - Egg protein
  - Polyvinyl chloride
- Biologic enzymes
- *Bacillus subtilis* (laundry detergent workers)
- Pancreatic enzymes
- Animal emanations
  - Canine or feline saliva
  - Horse dander (horse racing workers)
  - Rodent urine (laboratory animal workers)

Chest radiography can show transient or permanent infiltrates and central bronchiectasis, usually affecting the upper lobes (Figure 2.2). Advanced cases show extensive pulmonary fibrosis. Allergic bronchopulmonary aspergillosis is treated with systemic corticosteroids. Total serum IgE (increased to >1,000 kU/L

Box 2.6 • Diagnostic Features of Allergic Bronchopulmonary Aspergillosis

Clinical asthma

Bronchiectasis (usually proximal)

Increased total serum immunoglobulin (Ig) E

IgE antibody to *Aspergillus fumigatus* (by skin test or in vitro assay)[a]

Precipitins or IgG antibody to *Aspergillus*

Radiographic infiltrates (often in upper lobes)

Peripheral blood eosinophilia

[a] Required for diagnosis.

when active) may be helpful in following the course of the disease. Antifungal therapy alone has not been effective.

Medications for Asthma

Medications for asthma are listed in Box 2.7. They can be divided into bronchodilator compounds, anti-inflammatory compounds, and biologics. Poor inhaler technique and poor adherence to therapy can result in poor control of asthma. Therefore, all patients using a metered dose inhaler or dry powder inhaler should be taught the proper technique for using these devices. Patients using metered dose inhaled corticosteroids should use a spacer device with the inhaler.

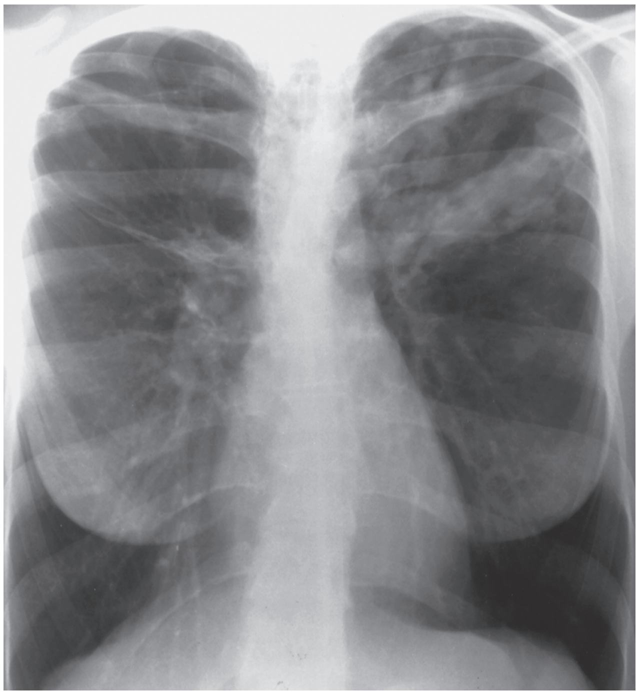

Figure 2.2. *Allergic Bronchopulmonary Aspergillosis. Chest radiograph shows cylindrical infiltrates involving the upper lobes.*

Box 2.7 • Medications for Asthma

- Bronchodilator compounds
  - Anticholinergic drugs (ipratropium bromide, tiotropium)
  - β_2-Agonist drugs
    - Short acting (albuterol, pirbuterol, levalbuterol)
    - Long acting (salmeterol, arformoterol, formoterol, indacaterol, vilanterol)
  - Methylxanthines (theophylline)
- “Antiallergic” compounds
  - Cromolyn
  - Nedocromil
- Glucocorticoids
  - Systemic
    - Prednisone
    - Methylprednisolone
  - Topical
    - Beclomethasone
    - Budesonide
    - Ciclesonide
    - Flunisolide
    - Fluticasone furoate
    - Fluticasone propionate
    - Mometasone
    - Triamcinolone acetonide
- Antileukotrienes
  - Leukotriene receptor antagonists (zafirlukast, montelukast)
  - Lipoxygenase inhibitors (zileuton)
- Glucocorticoids in combination with long-acting β_2-agonists
  - Budesonide with formoterol
  - Mometasone with formoterol
  - Fluticasone propionate with salmeterol
  - Fluticasone furoate with vilanterol
- Aeroallergen immunotherapy
- Biologics
  - Omalizumab
  - Mepolizumab
  - Reslizumab
  - Benralizumab

Bronchodilator Compounds

Both short- and long-acting anticholinergic drugs are available in the United States for asthma treatment. Ipratropium is a short-acting anticholinergic bronchodilator. It is available in an inhaler formulation and a nebulization formulation for use on an as-needed basis. Tiotropium is a long-acting anticholinergic bronchodilator. It can be used as an addition to the controller regimen for symptoms not controlled with inhaled corticosteroids and a long-acting β-agonist. Potential adverse effects include dry mouth and urinary retention.

A number of short-acting β-adrenergic compounds are available, but albuterol, levalbuterol, and pirbuterol are prescribed most often. More adverse effects occur when these medications are given orally than when they are given by inhalation. Nebulized β-agonists are rarely used long term in adult asthma, although they may be used in acute attacks. For home use, the metered dose inhaler or dry powder inhaler is the preferred delivery system. Salmeterol and formoterol are 2 long-acting inhaled β-agonists. Both should be used only in combination with inhaled corticosteroids. Theophylline is effective for asthma, but it has a narrow therapeutic index, and interactions with other drugs (cimetidine, erythromycin, and quinolone antibiotics) can increase the serum level of theophylline.

KEY FACTS

- ✓ Aspirin—can cause acute, severe, and fatal asthma in a small subset of patients with asthma
- ✓ Asthma plus cigarette smoking—leads to accelerated chronic obstructive pulmonary disease
- ✓ Occupational asthma—accounts for about 6% to 15% of all adult-onset asthma
- ✓ Allergic bronchopulmonary aspergillosis—typically presents as severe corticosteroid-dependent asthma
- ✓ Ipratropium bromide—the only anticholinergic drug available in the United States for treating asthma

Anti-inflammatory Compounds

Cromolyn and nedocromil are inhaled anti-inflammatory (mast cell–stabilizing) medications that are appropriate for treatment of mild asthma. The 5-lipoxygenase inhibitor zileuton and the leukotriene receptor antagonists zafirlukast and montelukast are approved for treatment of mild persistent asthma. These agents work by decreasing the inflammatory effects of leukotrienes. Zileuton can cause increased liver function test results. Cases of Churg-Strauss vasculitis have also been linked to zafirlukast and montelukast, although a clear cause-and-effect relationship has not been established.

Corticosteroids

Many experts recommend inhaled glucocorticoids for all severities of persistent asthma because of the potential long-term benefits of reduced bronchial hyperresponsiveness and reduced airway remodeling (fibrosis). Long-term use of β-agonist bronchodilators alone may adversely affect asthma; this also argues for earlier use of inhaled glucocorticoids. Asthma death has been linked to the heavy use of β-agonist inhalers, but this effect appears to be mitigated when inhaled corticosteroids are used concomitantly.

Box 2.8 • Benefits of Corticosteroids in Treatment of Asthma

Reduce airway inflammation by modulating cytokines interleukin (IL)-4 and IL-5

Can inhibit inflammatory properties of monocytes and platelets

Increase eosinophil apoptosis

Have vasoconstrictive properties

Decrease mucous gland secretion

The inflammatory infiltrate in the bronchial submucosa of patients with asthma probably depends on cytokine secretory patterns. Corticosteroids may interfere at several levels in the cytokine cascade, and they offer several benefits (Box 2.8).

The most common adverse effects of inhaled corticosteroids are dysphonia and thrush. These unwanted effects occur in about 10% of patients and can be reduced by using a spacer device and rinsing the mouth after administration. Usually, oral thrush can be treated successfully with oral antifungal agents. Dysphonia, when persistent, may be treated by decreasing or discontinuing the use of inhaled corticosteroids.

Detailed study of the systemic effects of inhaled corticosteroids shows that these agents are much safer than oral corticosteroids. Nevertheless, there is evidence that high-dose inhaled corticosteroids can affect the hypothalamic-pituitary-adrenal axis and bone metabolism. Also, high-dose inhaled corticosteroids may increase the risk of glaucoma, cataracts, and osteoporosis. Inhaled corticosteroids can decrease growth velocity in children and adolescents. The effect of inhaled corticosteroids on final adult height is not known but appears to be minimal.

Box 2.9 • Goals of Asthma Management

No asthma symptoms

No asthma attacks

Normal activity level

Normal lung function

Use of safest and least amount of medication necessary

Establishment of therapeutic relationship between patient and provider

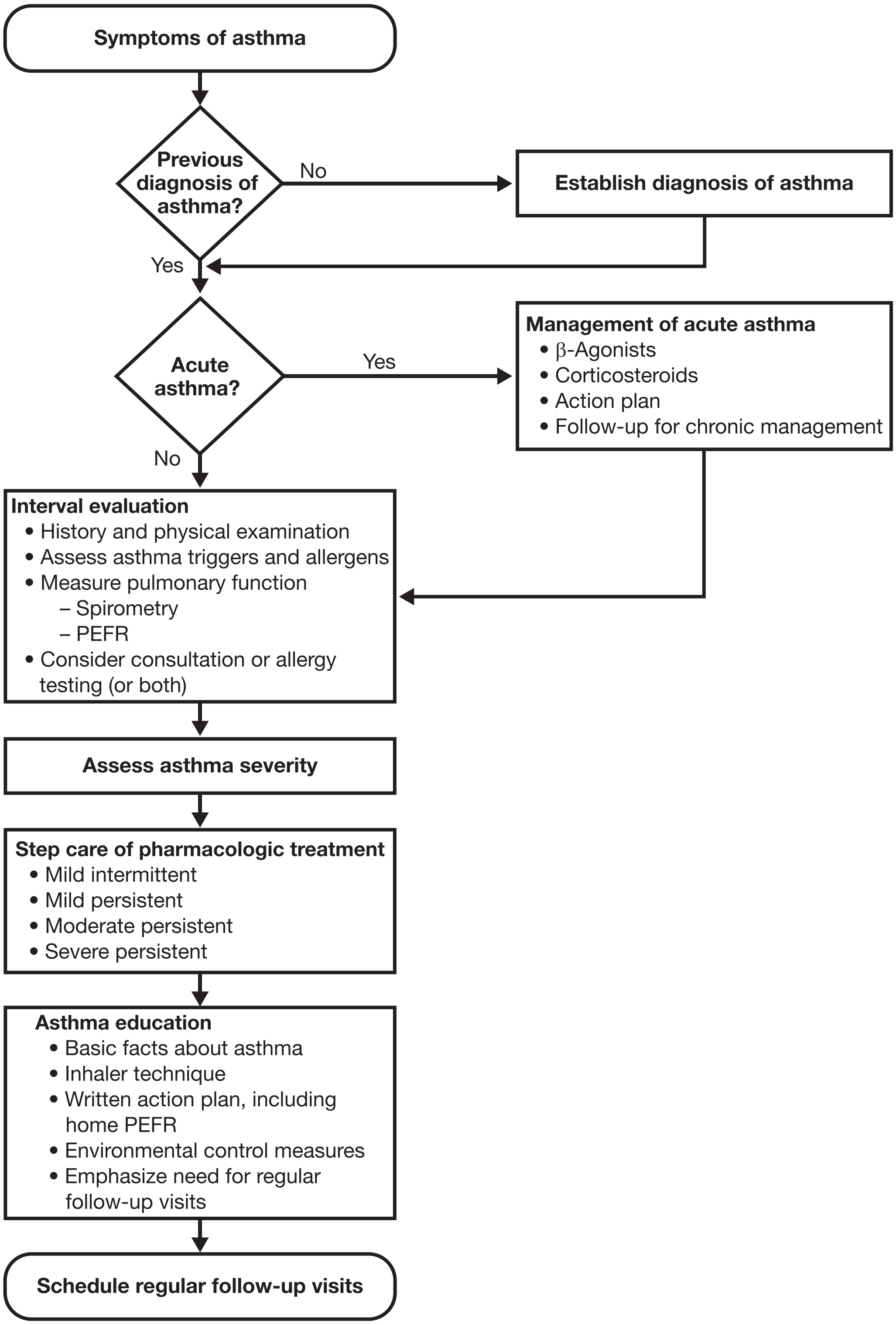
Symptoms of asthma
Previous diagnosis of asthma?
No
Establish diagnosis of asthma
Yes
Acute asthma?
Yes
Management of acute asthma
• β-Agonists
• Corticosteroids
• Action plan
• Follow-up for chronic management
No
Interval evaluation
• History and physical examination
• Assess asthma triggers and allergens
• Measure pulmonary function
– Spirometry
– PEFR
• Consider consultation or allergy testing (or both)
Assess asthma severity
Step care of pharmacologic treatment
• Mild intermittent
• Mild persistent
• Moderate persistent
• Severe persistent
Asthma education
• Basic facts about asthma
• Inhaler technique
• Written action plan, including home PEFR
• Environmental control measures
• Emphasize need for regular follow-up visits
Schedule regular follow-up visits

Figure 2.3. *Diagnosis and Management of Asthma. PEFR indicates peak expiratory flow rate.*

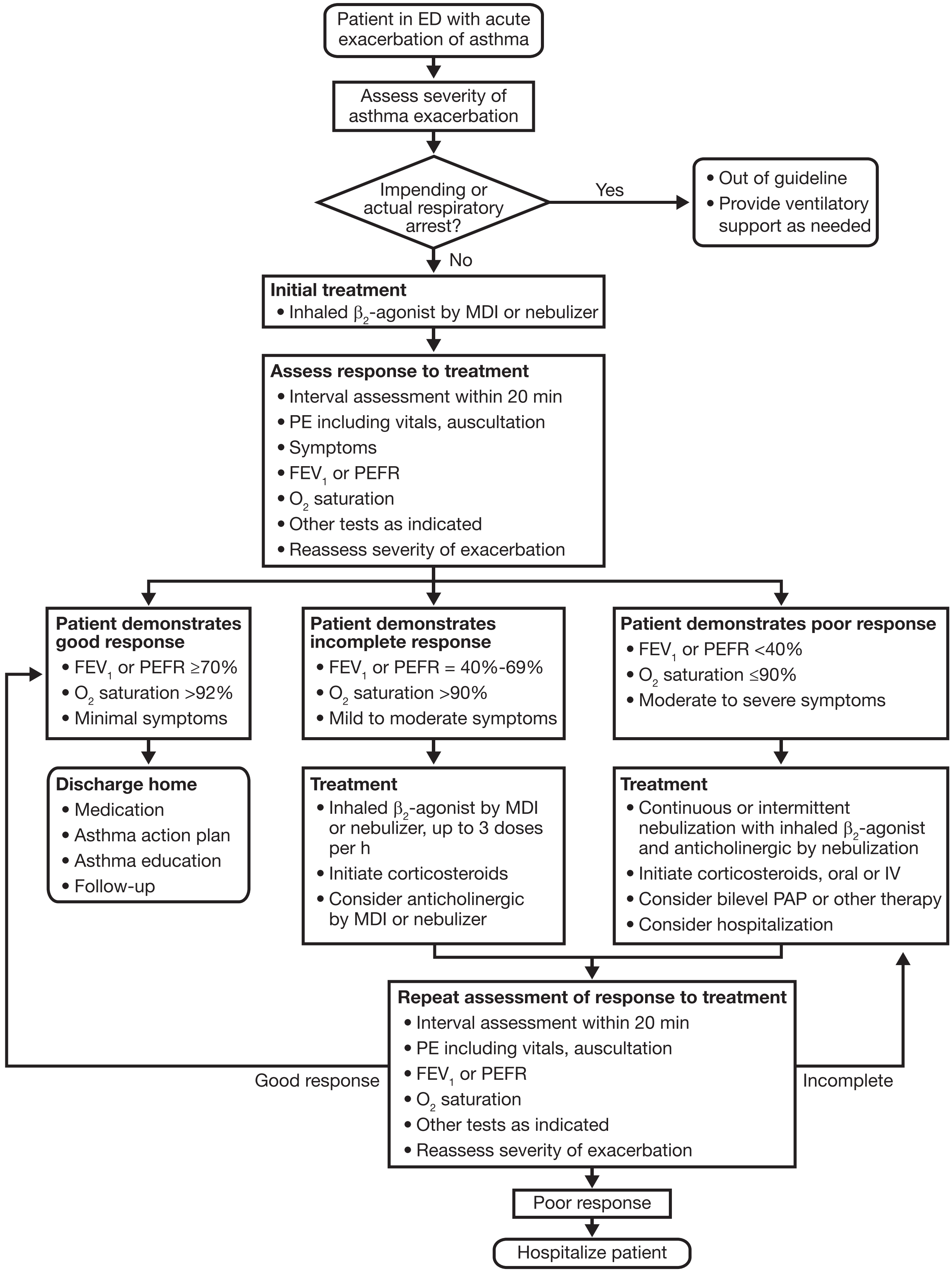
Patient in ED with acute exacerbation of asthma
Assess severity of asthma exacerbation
Impending or actual respiratory arrest?
Yes
• Out of guideline
• Provide ventilatory support as needed
No
Initial treatment
• Inhaled β_2-agonist by MDI or nebulizer
Assess response to treatment
• Interval assessment within 20 min
• PE including vitals, auscultation
• Symptoms
• FEV_1 or PEFR
• O_2 saturation
• Other tests as indicated
• Reassess severity of exacerbation
Patient demonstrates good response
• FEV_1 or PEFR ≥70%
• O_2 saturation >92%
• Minimal symptoms
Patient demonstrates incomplete response
• FEV_1 or PEFR = 40%-69%
• O_2 saturation >90%
• Mild to moderate symptoms
Patient demonstrates poor response
• FEV_1 or PEFR <40%
• O_2 saturation ≤90%
• Moderate to severe symptoms
Discharge home
• Medication
• Asthma action plan
• Asthma education
• Follow-up
Treatment
• Inhaled β_2-agonist by MDI or nebulizer, up to 3 doses per h
• Initiate corticosteroids
• Consider anticholinergic by MDI or nebulizer
Treatment
• Continuous or intermittent nebulization with inhaled β_2-agonist and anticholinergic by nebulization
• Initiate corticosteroids, oral or IV
• Consider bilevel PAP or other therapy
• Consider hospitalization
Repeat assessment of response to treatment
• Interval assessment within 20 min
• PE including vitals, auscultation
• FEV_1 or PEFR
• O_2 saturation
• Other tests as indicated
• Reassess severity of exacerbation
Good response
Incomplete
Poor response
Hospitalize patient

Figure 2.4. Management of Acute Asthma in Adults. ED indicates emergency department; FEV_1, forced expiratory volume in 1 second; IV, intravenous; MDI, metered dose inhaler; O_2, oxygen; PAP, positive airway pressure; PE, physical examination; PEFR, peak expiratory flow rate.

(Modified from Sveum R, Bergstrom J, Brottman G, Hanson M, Heiman M, Johns K, et al. Diagnosis and management of asthma. 10th ed. Bloomington [MN]: Institute for Clinical Systems Improvement; c2012. p 2. [cited 2018 Mar 12; updated 2012 Jul.] Available from: http://www.icsi.org/_asset/rsjvnd/Asthma.pdf; used with permission.)

Biologics

Anti-IgE Treatment

Omalizumab was the first recombinant humanized anti-IgE monoclonal antibody approved for use in asthma. It blocks IgE binding to mast cells and is indicated for refractory moderate to severe persistent allergic asthma. It is approved for use in patients age 12 years or older who have positive results of skin or in vitro allergy testing to relevant allergens. Dosing is based on the patient's IgE level and body weight. The dosage is typically 150 to 375 mg subcutaneously every 2 to 4 weeks.

Anti–IL-5 Treatment

Mepolizumab, benralizumab, and reslizumab block IL-5, a potent chemoattractant for eosinophils. Anti–IL-5 treatment is indicated for moderate to severe persistent eosinophilic asthma.

Allergen Immunotherapy

Allergen immunotherapy can be used for mild persistent allergic asthma. It is not used in moderate to severe persistent asthma because of risk of an allergic reaction to the immunotherapy.

Asthma Management

The goals of asthma management are listed in Box 2.9.

Management of Chronic Asthma

Baseline spirometry is recommended for all patients with asthma, and home peak flow monitoring is recommended for those with moderate or severe asthma (Figure 2.3). An asthma questionnaire such as the Asthma Control Test can help objectify asthma control. In this questionnaire, a score of 20 or greater is considered good control. Environmental triggers and conditions contributing to asthma (AIR-SMOG; Box 2.4) should be discussed with all patients who have asthma, and allergy testing should be offered to those with suspected allergic asthma or with asthma that is not well controlled. An asthma action plan should be used. This includes outlining medication use at green, yellow, and red levels (similar to traffic light use of these colors) based on symptoms and peak flow readings.

Management of Acute Asthma

Inhaled β-agonists, measurements of lung function at presentation and during therapy, and systemic corticosteroids (for most adult patients) are the cornerstones of managing acute asthma (Figure 2.4). Generally, nebulized albuterol, administered repeatedly if necessary, is the first line of treatment. Delivery of β-agonist by metered dose inhaler can be substituted in less severe asthma attacks. Inhaled β-agonist delivered by continuous nebulization may be appropriate for more severe disease.

It is important to measure lung function (usually peak expiratory flow rate but also FEV_1 whenever possible) at presentation and after administration of bronchodilators. These measurements provide invaluable information that allows the physician to assess the severity of the asthma attack and the response (if any) to treatment.

Patients who do not have a prompt and full response to inhaled β-agonists should receive a course of systemic corticosteroids. Patients with the most severe and poorly responsive disease (FEV_1 <50%, oxygen saturation <90%, and moderate to severe symptoms) should be treated on a hospital ward or in an intensive care unit.

KEY FACTS

- ✓ Cromolyn and nedocromil—inhaled anti-inflammatory drugs appropriate for treating mild or moderate asthma
- ✓ Inhaled glucocorticoids—recommended for all severity levels of persistent asthma because of potential long-term benefits (reduced bronchial hyperresponsiveness, reduced airway remodeling)
- ✓ Omalizumab—first recombinant humanized anti-IgE monoclonal antibody approved for use in asthma
- ✓ Baseline spirometry—recommended for all patients with asthma; home peak flow monitoring recommended for those with moderate or severe asthma
- ✓ Cornerstones of managing acute asthma—inhaled β-agonists, lung function measurements (at presentation, during therapy), and systemic corticosteroids (for most patients)
- ✓ Systemic corticosteroid—full course recommended if response to inhaled β-agonists is not prompt and full

I

Questions and Answers

Questions

Multiple Choice (Choose the best answer)

I.1. A 62-year-old man presents with a 3-year history of recurrent sinopulmonary infections documented by sinus computed tomography and chest radiographs. He does not recall any history of recurrent infections, allergic rhinitis, or asthma before the past 3 years. Sputum cultures have shown growth of *Streptococcus pneumoniae* and *Haemophilus influenzae*. Currently, he notes a chronic productive cough. Which one of the following laboratory tests is most likely to be abnormal in this patient?

a. Immunoglobulin (Ig) G level
b. Neutrophil chemotaxis assay
c. Total complement level
d. IgE level

I.2. A 38-year-old woman reports having widespread hives, wheeze, and feeling faint within 10 minutes of being stung by an insect. She was seen in the emergency department, received a diagnosis of anaphylaxis, and was treated with epinephrine and antihistamines, with gradual resolution of her symptoms. Given her activity, she feels she is likely to be stung again in the future. What would be most helpful to *prevent* a future anaphylactic reaction?

a. Use of a daily nonsedating antihistamine
b. Carrying injectable epinephrine
c. Testing to identify the culprit and receipt of corresponding immunotherapy
d. Education on avoidance of stinging insects

I.3. A 55-year-old man notes gradual worsening of his asthma and the development of chronic nasal congestion, postnasal drainage, and decreased sense of smell over the past year. On physical examination, he has bilateral nasal polyps. Sinus computed tomography shows considerable inflammation in all the sinuses. A complete blood cell count with differential is normal except for an increased eosinophil count of 0.7 eosinophils/mL (reference range, 0.1-0.5 eosinophils/mL). The primary treatment of his condition would be which of the following?

a. Systemic and topical corticosteroid
b. Antihistamine
c. Long-term, daily, low-dose antibiotic
d. Leukotriene blocker

I.4. A 47-year-old woman with a history of moderate persistent asthma continues to be symptomatic with wheeze and shortness of breath, despite the use of a medium-dose inhaled corticosteroid and long-acting β-agonist (ICS/LABA) and montelukast. Adherence and inhaler technique are good. Possible contributors, including rhinitis and gastroesophageal reflux, are well controlled. Which medication would be most beneficial to add or exchange to control symptoms?

a. Zileuton
b. Albuterol/ipratropium
c. High-dose ICS/LABA
d. Tiotropium

I.5. A 54-year-old man with a history of moderate persistent asthma has worsening of his asthma despite aggressive topical management that includes high-dose inhaled corticosteroid and long-acting β-agonist (ICS/LABA), montelukast, and tiotropium. He has been treated with multiple prednisone bursts, with initial improvement in his symptoms, then recurrence when not taking the prednisone. Adherence and inhaler technique are good. Possible contributors, including rhinitis and gastroesophageal reflux, are well managed. He is not taking any asthma-provoking medications. On physical examination, expiratory wheezes are heard through all lung fields. Spirometry shows forced expiratory volume in 1 second (FEV_1) to forced vital capacity ratio (FEV_1/FVC) of 48%; FEV_1 is 35% of predicted. Chest radiograph shows upper lobe infiltrates. Which of the following is required to make the specific diagnosis?

a. Increased immunoglobulin (Ig) E >1,000 kU/L
b. IgE antibody to *Aspergillus fumigatus* by skin test or in vitro assay
c. Increased eosinophil count >0.75 eosinophil/mL
d. Presence of bronchiectasis

I.6. A 24-year-old man has wheezing and shortness of breath when exercising. He also has these symptoms during an upper respiratory infection. Otherwise, the patient does not note any respiratory symptoms. On physical examination, his lung examination is normal. Spirometry shows a normal baseline forced expiratory volume in 1 second (FEV_1) to forced vital capacity ratio (FEV_1/FVC) and normal FEV_1. Methacholine challenge shows a 24% drop in FEV_1. He has not received any prior treatment for his symptoms. Exercise-induced asthma is suspected. What would be the first line of treatment?

a. Montelukast daily
b. Albuterol inhaler, before exercise
c. Low-dose inhaled fluticasone and salmeterol inhaler daily
d. Salmeterol inhaler daily

Answers

I.1. Answer a.

The patient presents with recurrent sinopulmonary infections with encapsulated organisms consistent with common variable immune deficiency (CVID). The primary laboratory abnormality in CVID is a decreased IgG level. The neutrophil chemotaxis assay would be abnormal in chronic granulomatous disease that would present at an earlier age and present with lung and skin abscesses. Abnormalities in complement can include severe recurrent infections, usually with concomitant connective tissue disease. A markedly elevated IgE level can be seen in Job syndrome, manifest by severe eczema and recurrent infection beginning in childhood.

I.2. Answer c.

The patient had an anaphylactic reaction to a stinging insect. With a subsequent sting, she would have approximately a 65% chance of another anaphylactic reaction. Immunotherapy to the causative insect (typically yellow jacket, hornet, wasp, or bee) decreases the risk to approximately 5%. This would be most helpful to prevent a future reaction. There is no indication for daily nonsedating antihistamine because it would not prevent an anaphylactic reaction with exposure. The patient should carry injectable epinephrine as an immediate treatment of a sting reaction. Education is also helpful but not on the same order.

I.3. Answer a.

The patient has a combination of asthma, nasal polyps, and chronic sinus inflammation. These are caused primarily by eosinophilic inflammation and respond well to treatment with corticosteroids. Treatment initially would include both systemic and topical corticosteroid therapy. Antihistamines are not typically helpful in this condition. Studies evaluating long-term, daily, low-dose antibiotic treatment have had mixed results. Leukotriene blockers are potentially helpful, especially in the patient subgroup that also has aspirin sensitivity.

I.4. Answer d.

The patient continues to be symptomatic despite step 4 treatment. Possible contributors have been assessed. From a medication standpoint, the next step would be the addition of the long-acting anticholinergic bronchodilator tiotropium, per global initiative for asthma guidelines. High-dose ICS/LABA would be the next option, followed by the biologics. Zileuton would not be expected to result in clinically significant improvement given the patient is already taking montelukast. Albuterol/ipratropium is formulated for use on an as-needed basis and is not part of a daily controller regimen in asthma.

I.5. Answer b.

The patient has allergic bronchopulmonary aspergillosis (ABPA). This is a hypersensitivity response to *Aspergillus* that results in severe, difficult-to-treat asthma. To make the diagnosis, an IgE sensitivity to *Aspergillus* must be present. A number of other findings seen in ABPA include increased IgE, particularly when ABPA is active; eosinophilia; IgG antibody to *Aspergillus*; radiographic chest infiltrates; and bronchiectasis. However, these other results, although often present, are not absolutely required to make the diagnosis.

I.6. Answer b.

The patient exhibits exercise-induced asthma but otherwise does well. The first-line treatment for exercise-induced asthma is pretreatment with albuterol before exercise. Montelukast also has been shown to provide benefit for exercise-induced asthma, but it is not the first-line treatment. Inhaled corticosteroids generally are not helpful in exercise-induced asthma but can be beneficial if the patient has underlying persistent asthma. Salmeterol or other long-acting β-agonists taken on a daily basis are contraindicated for an asthmatic patient unless given concomitantly with an inhaled corticosteroid.

Section
II

Cardiology

3

Arrhythmias and Syncope

PETER A. NOSEWORTHY, MD

Mechanism of Arrhythmias

Cardiac arrhythmias are due to disorders of impulse propagation (reentry) or impulse formation (abnormal automaticity or triggered activity). Reentry is the most common mechanism of arrhythmia and is further classified as *macroreentrant* or *microreentrant*. Macroreentrant arrhythmias have a discrete, definable circuit such as atrioventricular (AV) reentrant tachycardia (which are sustained as the impulse propagates across atrial, AV nodal, ventricular, accessory pathway, and back to the atrial tissue) or ventricular tachycardia (most often sustained around or through an area of myocardial scar). Microreentry occurs within a very small circuit and thus appears to arise from a single point in the myocardium. Three conditions are needed for reentry to occur: 1) more than 2 anatomically or functionally distinct pathways (eg, AV nodal reentry via slow and fast AV nodal pathways), 2) transient, unidirectional block in 1 pathway, and 3) slowed conduction in 1 pathway that allows the impulse to reenter the other (previously blocked) pathway or limb of the circuit.

Automatic arrhythmias result from a single myocardial focus that has enhanced impulse formation activity and are often more sensitive to sympathetic tone, hypoxia, acid-base and electrolyte disturbances, or atrial or ventricular stretch (eg, exacerbations of congestive heart failure). Triggered arrhythmias result from membrane potential oscillations following an action potential (so-called afterdepolarizations) that reach threshold and result in impulse formation. A common triggered arrhythmia is digoxin toxicity or ventricular fibrillation that occurs in the clinical setting of a prolonged QT interval.

Evaluation of Suspected Rhythm Disorders

Electrocardiography

Electrocardiography (ECG) is a simple and cost-effective tool for evaluating rhythm disorders. Most arrhythmias can be diagnosed on ECG and, even between episodes, it can provide important clues to the predisposing substrate (eg, ventricular preexcitation in Wolff-Parkinson-White [WPW] syndrome or repolarization abnormalities in long QT syndrome).

Ambulatory ECG Monitoring

Ambulatory ECG (Holter) monitoring allows evaluation of rhythm disturbances and their relationship to daily activities. It is useful to have patients keep a diary and correlate symptoms with the recorded heart rhythm. Normal results on Holter monitoring, however, do not rule out infrequent arrhythmias. Ambulatory ECG monitoring is also useful for assessing the impact of medical or ablative therapies.

Event Recording

Event recorders are useful for documenting rhythm when episodes are less frequent (<1 episode per 24 to 48 hours) but the events are symptomatic. The device is activated by the patient during symptoms. Continuous loop recorders record the ECG obtained 30 seconds to 4 minutes before the activation button is depressed and can thus be used to record events in which the patient can only trigger the device after the event (arrhythmias that cause syncope, for instance).

Implantable loop recorders can be implanted when symptoms are very infrequent (as infrequently as 1 or 2 times per year) and are programmed to record at prespecified thresholds or with patient-triggered events. Although costly, these implanted devices have a battery life of 2 to 3 years and are very useful in achieving symptom-rhythm correlation for infrequent episodes.

Electrophysiologic Testing

Electrophysiologic (EP) testing is an invasive method that is useful for assessing the substrate for arrhythmia. Indications for EP testing include palpitations likely due to a cardiac rhythm disorder (supraventricular tachycardia or ventricular tachycardia) or syncope suggestive of a cardiogenic mechanism. It can be used in combination with tilt-table testing for the evaluation of patients with suspected cardioinhibitory or vasodepressor syncope or the evaluation of abnormal postural blood pressure and heart rate responses. EP testing is not required in most patients with symptomatic bradycardia, especially in those for whom a permanent pacemaker is already indicated.

KEY FACTS

- ✓ Reentry—most common mechanism of arrhythmia; classified as macroreentrant or microreentrant
- ✓ Three conditions needed for reentry to occur—1) more than 2 anatomically or functionally distinct pathways, 2) transient, unidirectional block in 1 pathway, and 3) slowed conduction in second pathway that allows impulse to reenter previously blocked limb of circuit
- ✓ EP testing—invasive method useful for assessing substrate for arrhythmia
- ✓ EP testing—not required in most patients with symptomatic bradycardia for whom permanent pacemaker is indicated

Therapy for Heart Rhythm Disorders

Several therapeutic options are available for heart rhythm disorders. These include drug therapy, radiofrequency ablation or cryoablation, and device therapy (pacing for bradyarrhythmias and implantable cardioverter-defibrillators [ICDs] for tachyarrhythmias).

Antiarrhythmic Drugs

Antiarrhythmic drugs are frequently used as first-line therapy for rhythm control in atrial fibrillation, for the treatment of ventricular arrhythmia (often as an adjunct to ICD therapy), and occasionally for suppression of supraventricular arrhythmias.

Amiodarone

Amiodarone is highly effective, but its use is limited by multiple noncardiac adverse effects, including potential thyroid (hyperthyroidism and hypothyroidism), hepatic, ocular, and pulmonary toxicities. Nevertheless, amiodarone is generally considered reasonable in high-risk patients in whom the potential risks are justified. In patients with congestive heart failure (CHF), amiodarone has an essentially neutral effect on survival in patients at risk for fatal arrhythmias. It is not indicated for primary prevention of sudden death but is useful in avoiding continued ICD shocks in patients with a high burden of arrhythmia. Routine use of amiodarone after myocardial infarction or in unselected patients with CHF is not recommended.

Adenosine

Adenosine can terminate reentrant tachycardia that relies on conduction through the AV node by interrupting AV node conduction. It has a half-life of 10 seconds. Adenosine will not terminate arrhythmias such as atrial fibrillation or flutter in which the AV node is not a critical part of the reentrant circuit, but it may help in diagnosis of these arrhythmias (ie, by slowing AV conduction to allow visualization of flutter waves). Adenosine may terminate some ventricular arrhythmias (adenosine-sensitive ventricular tachycardia) that originate from the right ventricular outflow tract, but this is an uncommon clinical entity. Adenosine (and verapamil) is contraindicated in patients presenting with a wide QRS tachycardia and atrial fibrillation associated with WPW syndrome because of the risk of rapid conduction across the accessory pathway (which is not sensitive to adenosine) and induction of ventricular fibrillation.

Adverse Effects of Antiarrhythmic Drugs

Most antiarrhythmic drugs can have proarrhythmic effects. The most worrisome proarrhythmic effect, increased ventricular arrhythmia, can sometimes limit antiarrhythmic drug use in patients with structural heart disease. A classic example of proarrhythmia is quinidine syncope, in which polymorphic ventricular tachycardia results in repeated syncopal events after initiation of quinidine therapy (Figure 3.1).

Radiofrequency Ablation

Radiofrequency ablation has revolutionized the treatment of heart rhythm disorders. Supraventricular tachycardias, such as AV nodal reentrant tachycardia or tachycardia due to an accessory pathway (eg, WPW syndrome), are curable with radiofrequency ablation in more than 95% of cases. Atrial tachycardias are curable in 70% to 90% of cases. Table 3.1 lists arrhythmias amenable to catheter ablation therapy. Atrial fibrillation (especially paroxysmal atrial fibrillation)

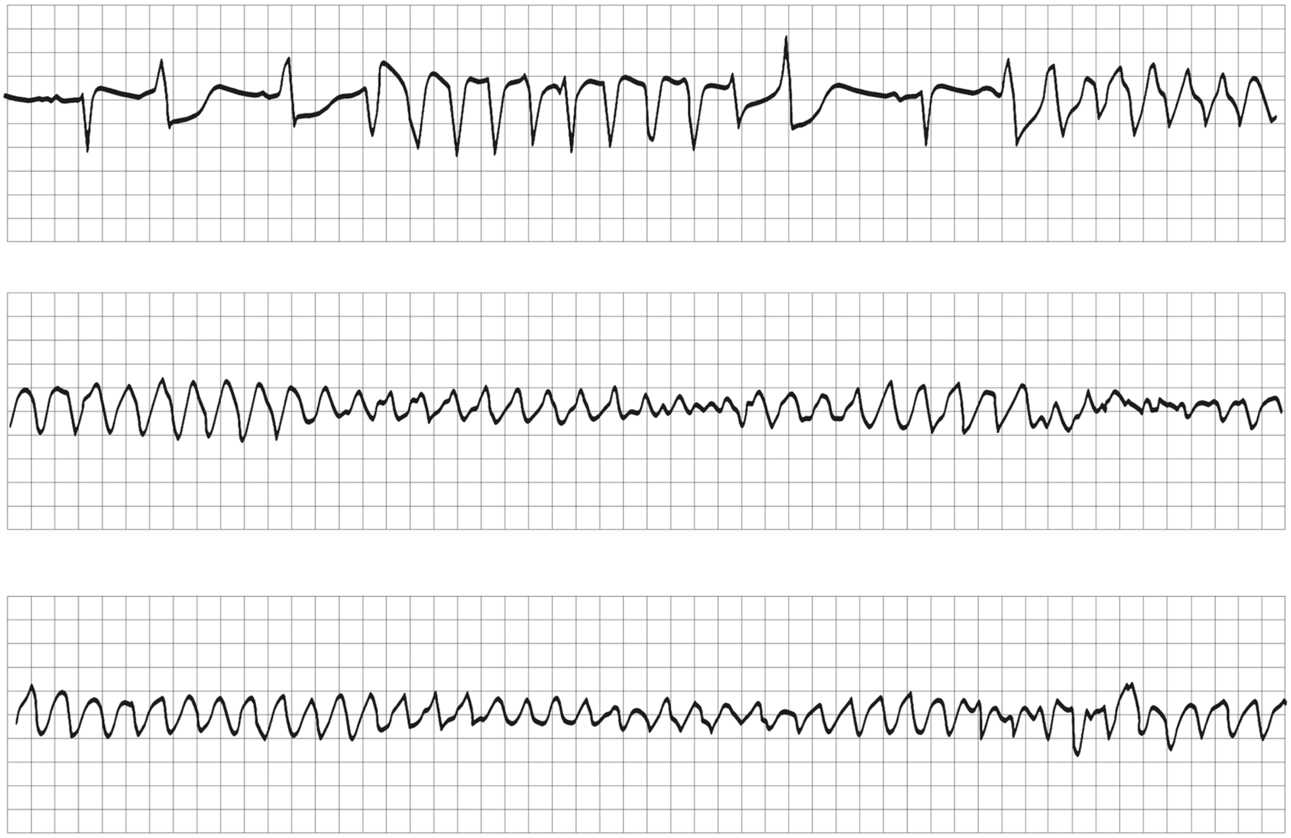

Figure 3.1. Proarrhythmic Response to Quinidine. Quinidine resulted in prolongation of QT interval, and late-coupled premature ventricular complex initiated polymorphic ventricular tachycardia, termed torsades de pointes.

and ventricular tachycardia (either reentrant or automatic) can also be successfully treated with radiofrequency ablation; however, success rates are lower than for most supraventricular tachycardias. Among others, complications include vascular injury, cardiac perforation, and cardioembolic stroke that, together, occur in 1% to 4% of patients. Occasionally, the target of ablation may be in proximity to the AV node (eg, parahisian accessory pathways) and ablation may be associated with a risk of complete heart block requiring pacemaker implantation.

Table 3.1 • Heart Rhythms Amenable to Catheter Ablation

Rhythm	Curable	Treatable
SVT	AVNRT	AF
	AVRT (bypass tract)	
	EAT	
	AFL (without fibrillation)	
Ventricular	RV outflow tract tachycardia Idiopathic LV tachycardia	VT due to coronary disease and scar after MI

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; AVNRT, atrioventricular node reentry tachycardia; AVRT, atrioventricular reentry tachycardia; EAT, ectopic atrial tachycardia; LV, left ventricular; MI, myocardial infarction; RV, right ventricular; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

Device Therapy

Device therapy is appropriate for symptomatic bradycardia (permanent pacemaker) and for the primary and secondary prevention of sudden cardiac death (ICD). Indications for a permanent pacemaker implantation in specific conduction system diseases are listed in Box 3.1.

Box 3.1 • Indications for Pacemaker Implantation

- Sinus node dysfunction
  - Class I
    - Documented symptomatic bradycardia
  - Class II
    - HR <40 bpm, symptoms present but not clearly correlated with bradycardia
  - Class III
    - Asymptomatic bradycardia (HR <40 bpm)
- AV block
  - Class I
    - Symptomatic 2° or 3° AV block, permanent or intermittent
    - Congenital 3° AV block with wide QRS
    - Advanced AV block 14 days after cardiac surgery
  - Class II
    - Asymptomatic type II 2° or 3° AV block with ventricular rate >40 bpm
  - Class III
    - Asymptomatic 1° and type I 2° AV block
- Myocardial infarction
  - Class I
    - Recurrent type II 2° AV block and 3° AV block with wide QRS
    - Transient advanced AV block in presence of BBB
  - Class II
    - Persistent advanced AV block with narrow QRS
    - Acquired BBB in absence of AV block
  - Class III
    - Transient AV block in absence of BBB

Abbreviations: AV, atrioventricular; BBB, bundle branch block; bpm, beats per minute; HR, heart rate.

Permanent Pacemaker Implantation

An internationally used 4-letter system is applied to classify different types of permanent pacemakers (Table 3.2). The choice of the device used depends on the clinical circumstances.

In general, all pacemakers pace the heart if the heart rate falls below a programmed lower rate limit. Dual-chamber pacemakers allow sequential atrial and ventricular pacing (as opposed to ventricular pacing, which can be asynchronous with the atrial impulse) or tracking of atrial rhythms to the ventricle in cases of heart block. Physiologic pacing attempts to maintain heart rate with normal AV synchrony and to increase heart rate in response to physical activity and can be used to treat chronotropic incompetence (inability to reach a heart rate required for physical activity). Patients fitted with this type of pacemaker may have improved exercise endurance during treadmill testing. A sensor that responds to body motion, respiratory rate, cardiac contractility, or other variables can be used to drive the pacemaker so that the rate at which pacing occurs is appropriate to metabolic demands.

Early complications (within 30 days of implantation) are usually related to vascular injury, hematoma, pneumothorax, dislodgment of the lead, and extracardiac stimulation. *Late complications* include lead fracture or insulation defect, infection, pacemaker syndrome (simultaneous atrial and ventricular contraction resulting in symptomatic cannon A waves), and pacemaker-mediated tachycardia.

Pacemaker-mediated tachycardia is a well-recognized complication of dual-chamber pacemakers (DDD pacing). It occurs during DDD pacing when there is intact retrograde conduction between the ventricle and atrium. A spontaneous premature ventricular contraction occurs that conducts retrogradely to the atrium and is then tracked to the ventricle. This sets up an endless loop tachycardia. The tachycardia rate is typically close to the upper rate limit of the device. Most pacemakers can recognize and attempt to abort pacemaker-mediated tachycardia, or it can be avoided by programming changes of the pacemaker generator that result in the device ignoring the retrograde atrial impulse.

Implantable Cardioverter-Defibrillator

An ICD continuously monitors heart rhythm and can detect and treat abnormal ventricular arrhythmia with overdrive pacing (antitachycardia pacing, which is painless) or with up to 40-J shocks. ICDs have been shown to reduce mortality rates among patients who survive sudden cardiac death and in those at high risk for sudden death (most typically those with an ejection fraction <35%). Some common indications for ICD implantation are listed in Box 3.2.

Table 3.2 • Code of Permanent Pacing

Chamber(s) Paced	Chamber(s) Sensed	Mode(s) of Response	Programmable Capabilities
V = ventricle	V = ventricle	T = triggered	R = rate modulated
A = atrium	A = atrium	I = inhibited	
D = dual (atrium and ventricle)	D = dual (atrium and ventricle) O = none	D = dual (triggered and inhibited) O = none	

KEY FACTS

- ✓ Therapeutic options for heart rhythm disorders—drug, radiofrequency ablation or cryoablation, device
- ✓ Adenosine (and verapamil)—contraindicated for wide QRS tachycardia and atrial fibrillation with WPW syndrome
- ✓ Transcatheter radiofrequency ablation—cures narrow complex tachycardias in >95% of cases and atrial tachycardias in >90% of cases
- ✓ Pacemaker implantation, early complications (≤30 days of implantation)—usually related to vascular injury, hematoma, pneumothorax, dislodgment of lead, extracardiac stimulation
- ✓ Pacemaker implantation, late complications—lead fracture or insulation defect, infection, pacemaker syndrome, pacemaker-mediated tachycardia

Specific Arrhythmias

The Bradycardias

Bradycardia is defined as a heart rate less than 60 beats per minute (bpm) at rest. Bradycardia can be a normal finding (associated with high vagal tone in asymptomatic and often fit and healthy persons), can be related to a diseased sinus node (sinus node dysfunction), or can be due to other causes (eg, drug therapy, conduction disease with heart block, myocardial infarction).

Box 3.2 • Indications for Placement of an Implantable Cardioverter-Defibrillator

Secondary prevention

- Cardiac arrest caused by ventricular fibrillation or ventricular tachycardia in the absence of acute ischemia or other reversible cause

Primary prevention

- Known conditions with a high risk of life-threatening ventricular tachycardia (eg, high-risk patients with long QT syndrome or hypertrophic cardiomyopathy)
- Ischemic and nonischemic cardiomyopathy (LVEF <35%) plus congestive heart failure (NYHA class II or III)
- Ischemic cardiomyopathy due to prior myocardial infarction and LVEF <30%

Abbreviations: LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Key Definition

Bradycardia: *heart rate <60 beats per minute at rest.*

Sinus Node Dysfunction

Sinus node dysfunction includes sinus bradycardia, sinus pauses, tachycardia-bradycardia syndrome (Figure 3.2), sinus arrest, and chronotropic incompetence. In most cases, sinus node dysfunction is diagnosed on the basis of the history and results of ECG and Holter monitoring. Invasive EP testing is usually not necessary. Prolonged monitoring with an event recorder may be required to correlate symptoms with bradycardia. Treadmill testing can distinguish true sinus node dysfunction (chronotropic incompetence in this case), in which a blunted heart rate occurs in response to exercise, from high vagal tone, in which the heart rate increases appropriately during exercise to meet metabolic need. EP testing is reserved for a smaller group of patients in whom the arrhythmia mechanism cannot be determined by noninvasive means.

Asymptomatic patients with sinus node dysfunction do not require specific therapy, whereas symptomatic patients usually require a pacemaker. Patients with tachycardia-bradycardia often have atrial fibrillation that can present with rapid ventricular rates or with symptomatic bradycardia. Pacemakers are used to prevent bradycardia and allow titration of medications to slow conduction through the AV node and to prevent episodes of rapid ventricular rate during atrial fibrillation.

Conduction System Disorders

A conduction system disorder occurs when impulses from the sinus node reaching the ventricle are delayed. Delay can occur in the right bundle (right bundle branch block), left bundle (left bundle branch block), or one of the hemifascicles of the left bundle (left anterior or posterior hemiblock). Bifascicular block usually refers to right bundle branch block with left anterior fascicular block (left axis deviation) or to right bundle branch block with left posterior fascicular block (right axis deviation). Patients presenting with syncope and bifascicular block may have intermittent complete heart block due to conduction system disease and may require pacing. Patients who have asymptomatic bifascicular block can usually be observed because progression to complete heart block is slow and may never occur in the majority of patients.

Conduction system disorders can be divided into first-degree, second-degree, and third-degree (complete) heart block.

First-Degree AV Block

In first-degree AV block, the PR interval on the ECG is prolonged (>200 milliseconds). In most cases, the block occurs in the AV node.

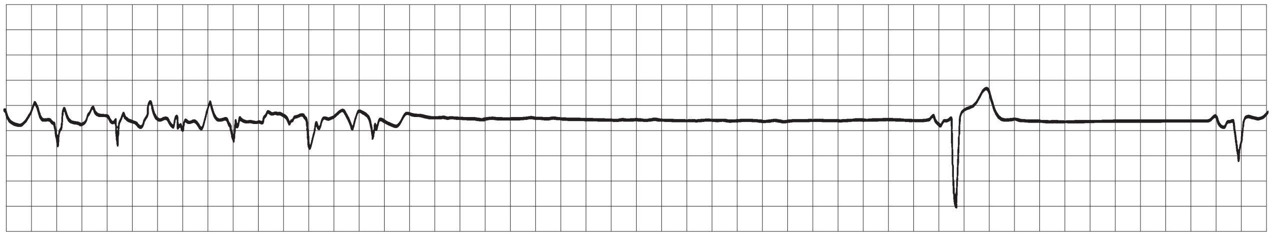

Figure 3.2. *Tachycardia-Bradycardia Syndrome. In this case, the episode of atrial fibrillation terminated spontaneously, followed by a 4.5-second pause until the sinus node recovered.*
(Adapted from MKSAP IX: Part C, Book 1, c1992. American College of Physicians; used with permission.)

Second-Degree AV Block

There are 2 subtypes of second-degree AV block: Mobitz I and Mobitz II. Mobitz I second-degree AV block (Wenckebach) manifests as gradual prolongation of the PR interval before a nonconducted P wave. The PR interval after the nonconducted P wave is shorter than the PR interval before the nonconducted P wave (Figures 3.3 and 3.4). The RR interval that encompasses the nonconducted P wave is shorter than 2 RR intervals between conducted beats (the long PR before the block “eats into” the RR interval). Wenckebach conduction occurs as a result of high vagal tone and often occurs after an inferior myocardial infarction or during vagal stimuli such as obstructive sleep apnea or vomiting. Wenckebach conduction almost never requires pacing.

Mobitz II second-degree AV block is caused by conduction block within the His-Purkinje system and may be associated with bundle branch block. The ECG shows a sudden failure of conduction of a P wave, with no change in the PR interval either before or after the nonconducted P wave (Figure 3.5). The ventricular escape rhythm is either a junctional escape focus, with a conduction pattern similar to that seen during normal rhythm, or a ventricular escape focus, with a wide QRS conduction pattern. Mobitz II block may herald complete heart block, and permanent pacing is often needed.

Third-Degree (Complete) Heart Block

Complete heart block is diagnosed when there is no relationship between atrial rhythm and ventricular rhythm, and atrial rhythm is faster than ventricular escape rhythm (Figure 3.6). The ventricular rhythm is usually regular. Treatment usually is permanent pacing.

Carotid Sinus Hypersensitivity Syndrome

Carotid sinus hypersensitivity is caused by serious bradycardia occurring during pressure of the carotid body (a 3-second pause or a decrease in systolic blood pressure of 50 mm Hg) (Figure 3.7). Carotid sinus hypersensitivity syndrome is common in elderly persons and can rarely be caused by anatomical abnormalities in the region of the carotid body (eg, lymph node enlargement, prior surgery). Most patients do not have spontaneous syncope, but those who do may require pacing. The abnormal response can be 1) pure cardioinhibitory manifested only by bradycardia, 2) pure vasodepressor manifested only with hypotension, or 3) combined cardioinhibitory-vasodepressor response. Permanent pacing treats only the cardioinhibitory response.

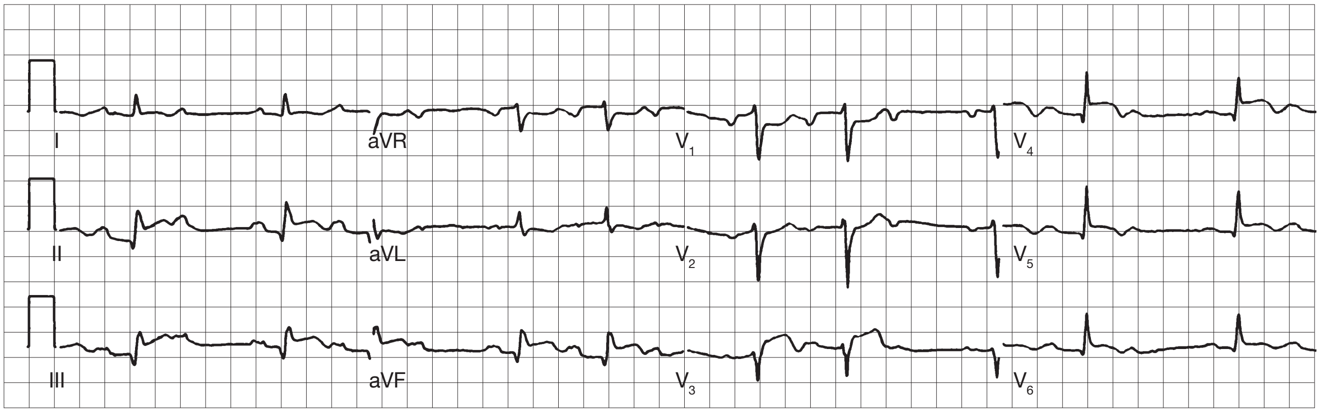

Figure 3.3. *3:2 Mobitz I (or Wenckebach) Second-Degree Atrioventricular Block. Patient had acute inferior myocardial infarction.*

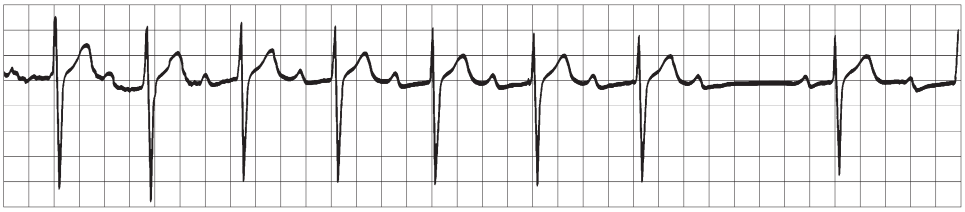

Figure 3.4. *Mobitz I Second-Degree Atrioventricular Block. Of note, gradual PR prolongation can be seen. PR interval after a nonconducted P wave is shorter than PR interval preceding the nonconducted P wave.*

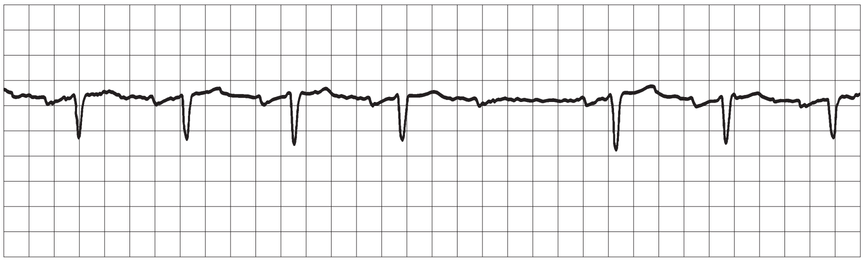

Figure 3.5. *Mobitz II Second-Degree Atrioventricular Block. No change occurred in the PR interval before or after a nonconducted P wave.*

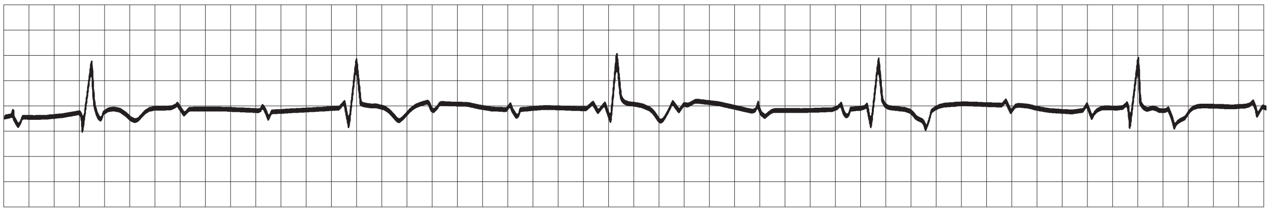

Figure 3.6. *Complete Heart Block. Atrial rate was 70 beats per minute and ventricular escape rhythm was 30 beats per minute.*

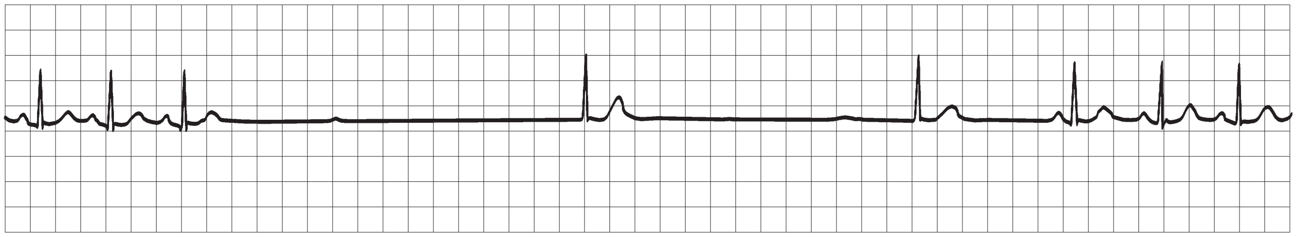

Figure 3.7. *Sinus Pause With Junctional Escape Beats Before Sinus Rhythm Returns. Test was done during carotid sinus massage.*

KEY FACTS

- ✓ First-degree AV block—PR interval on ECG is prolonged (>200 milliseconds)
- ✓ Second-degree AV block—2 subtypes are Mobitz I and Mobitz II
- ✓ Mobitz I block (Wenckebach)—gradual prolongation of PR interval before nonconducted P wave
- ✓ Mobitz II block—caused by conduction block within His-Purkinje system and may be associated with bundle branch block
- ✓ Third-degree (complete) heart block—no relationship between atrial rhythm and ventricular rhythm, and atrial rhythm is faster than ventricular escape rhythm
- ✓ Carotid sinus hypersensitivity—common in elderly persons and can rarely be caused by anatomical abnormalities in region of carotid body

The Tachycardias

Atrial Flutter

Atrial flutter is identified on the ECG by the characteristic sawtooth pattern of atrial activity at a rate of 240 to 320 bpm. Patients with normal conduction may have rapid ventricular rates (most often, 2:1 conduction with a rate of 150 bpm). Higher degrees of AV block (3:1 or higher) in the absence of drugs that slow AV nodal conduction (eg, digoxin, β-adrenergic blockers, calcium channel antagonists) suggest the presence of intrinsic AV conduction disease (Figure 3.8). In patients with 2:1 AV conduction, the flutter waves are often buried in the QRS complex. Carotid sinus massage (or transient AV node blockade with adenosine) may help reveal the flutter waves to establish the diagnosis.

Pharmacologic therapy for atrial flutter is used to slow AV node conduction and control the ventricular rate or to control the flutter itself. The same medications used to treat atrial fibrillation are used to treat atrial flutter. Catheter ablation targets the most common arrhythmia circuit around the tricuspid annulus and has a success rate of more than 90%.

Atrial Fibrillation

Atrial fibrillation, characterized by continuous and chaotic atrial activity, is the most common sustained arrhythmia. Its prevalence increases with age; 5% of patients age 65 years or older are affected. Common associated conditions include hypertension, cardiomyopathy, valvular heart disease (particularly mitral stenosis), sleep-disordered breathing, sick sinus syndrome, WPW syndrome (especially in young patients), alcohol use ("holiday heart"), and thyrotoxicosis.

The therapeutic approach to patients with atrial fibrillation is determined by the severity of symptoms and comorbid conditions. Therapeutic options include rate control (pharmacologic agents or ablation to slow AV node conduction), stroke prophylaxis in patients at risk for stroke, and rhythm control (treatments aimed at restoring and maintaining sinus rhythm). Stroke risk can be assessed using the CHA_2DS_2-VASc scoring system (1 point each for *c*ongestive heart failure, *h*ypertension, *a*ge ≥65 years, and *d*iabetes mellitus, *v*ascular disease, and female *s*ex and 2 points for previous *s*troke or transient ischemic attack and *a*ge ≥75 years). Anticoagulation is usually indicated if the CHA_2DS_2-VASc score is 2 or more (and can be considered if the CHA_2DS_2-VASc score is 1). Rhythm control is most appropriate in patients with symptoms due to atrial fibrillation despite adequate rate control but is generally not thought to reduce the mortality rate. In all patients, initial management should be rate control using AV nodal blocking agents and an assessment of stroke risk and need for anticoagulation before deciding on a long-term strategy. Pharmacologic agents useful for rate control and rhythm control are shown in Table 3.3.

Digoxin acts indirectly by increasing vagal tone and, at therapeutic concentration, has no direct effect in slowing AV node conduction. Because of its mechanism of action, digoxin is less

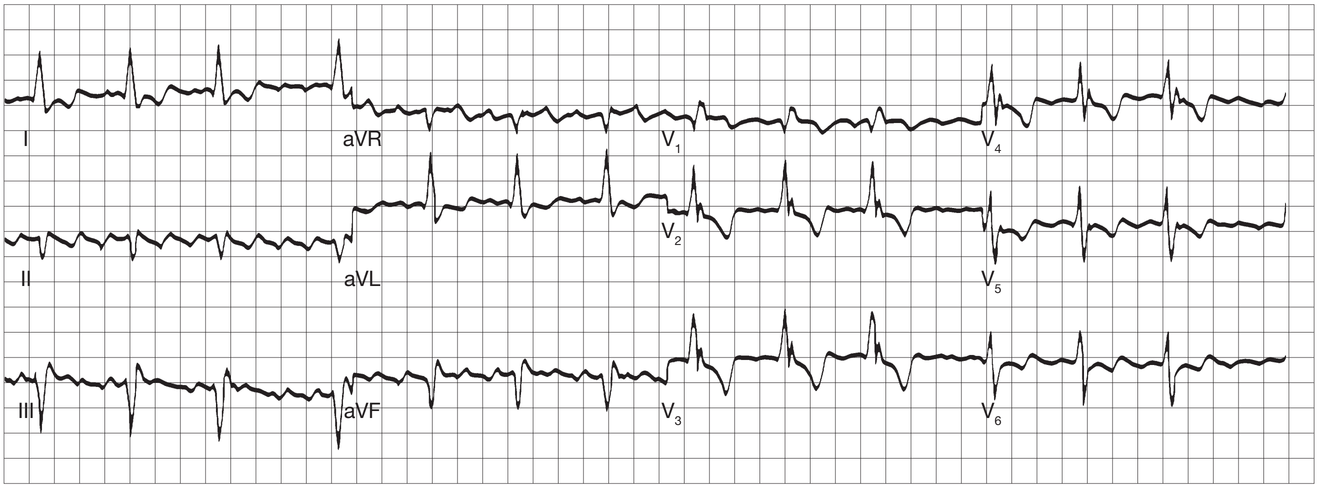

Figure 3.8. Atrial Flutter With 3:1 Conduction. Patient had atrioventricular conduction disease.

Table 3.3 • Pharmacologic Therapy for Atrial Fibrillation

Agents	Comments
Control of ventricular rate	
β-Blockers (eg, atenolol, metoprolol, propranolol, carvedilol)	Ideal postoperatively and in hyperthyroidism, acute MI, and chronic CHF (especially carvedilol)
Calcium channel blockers (eg, verapamil, diltiazem)	Nifedipine, amlodipine, and felodipine are not useful for slowing AV conduction
Digoxin	Less effective than β-blockers and calcium channel blockers, especially with exercise Useful in heart failure
Maintenance of sinus rhythm	
Class IA: quinidine, disopyramide, procainamide	Enhance AV conduction—rate must be controlled before use Monitor QTc
Class IC: propafenone, flecainide	Slow AV conduction Often first choice for patients with normal heart Monitor QRS duration
Class III: sotalol, amiodarone	Amiodarone is agent of choice for ventricular dysfunction and after MI

Abbreviations: AV, atrioventricular; CHF, congestive heart failure; MI, myocardial infarction.

effective than β-blockers or calcium channel blockers, particularly with exercise, when an increase in sympathetic tone results in more rapid AV node conduction. The optimal role for digoxin in atrial fibrillation is therapy for patients with left ventricular dysfunction (because of the drug's positive inotropy) or as adjunctive therapy for patients with chronic atrial fibrillation receiving β-blockers or calcium channel blockers. Digoxin alone is no better than placebo for terminating atrial fibrillation.

β-Blockers (eg, propranolol, metoprolol, atenolol) slow AV node conduction. They may be particularly useful when atrial fibrillation complicates hyperthyroidism or myocardial infarction.

Calcium channel blockers are divided into 2 groups: dihydropyridines (ie, nifedipine and amlodipine) and nondihydropyridines (ie, diltiazem and verapamil). Dihydropyridine agents have little or no effect on AV node conduction and no role in the management of atrial fibrillation. Verapamil and diltiazem are both available as intravenous and oral preparations and are well suited for acute and long-term rate control. Both agents have negative inotropic effects and must be used cautiously in CHF.

When pharmacologic rate control fails (due to persistent symptoms or intolerance of medications), catheter ablation of the AV junction may be considered as a "bail-out" rate control strategy. This approach is more than 95% effective for controlling symptoms and has minimal risk. The major disadvantage is creation of pacemaker dependence. In patients with paroxysmal atrial fibrillation, a dual-chamber pacemaker is implanted to allow AV synchrony during time of sinus rhythm. In patients with persistent atrial fibrillation, a single-chamber ventricular pacemaker (programmed to VVIR mode) is implanted. Dual-chamber pacemakers have a mode-switching function that permits tracking of P waves during sinus rhythm and reverts to VVIR (or DDIR) mode pacing when atrial fibrillation recurs.

Rhythm control (maintenance of sinus rhythm) is useful to manage symptoms attributable to atrial fibrillation. Common pharmacologic agents include the class IC antiarrhythmic agents propafenone and flecainide (sodium channel blockers) and the class II agents sotalol, dofetilide, and amiodarone (potassium channel blockers). Class IC agents are often used as first-line therapy because they are generally well tolerated and can be initiated in the outpatient setting, but these agents should be avoided in patients with structural heart disease (due to risk of proarrhythmia). Sotalol and dofetilide are generally safe in patients with prior myocardial infarction but necessitate hospitalization for initiation, to monitor for QT prolongation and risk of *torsades de pointes*. Amiodarone is an effective medication, but it has the potential for serious long-term adverse effects (thyroid, liver, and pulmonary toxicities among them).

Cardioversion for atrial fibrillation is commonly used when patients remain symptomatic despite efforts to achieve rate control. Patients with atrial fibrillation of more than 2 days in duration should receive anticoagulation before cardioversion. Warfarin therapy for 3 weeks before cardioversion substantially decreases the incidence of cardioversion-associated thromboembolism, and anticoagulation should be continued for a minimum of 4 weeks after cardioversion. Anticoagulation guidelines for atrial flutter are identical to those for atrial fibrillation. An alternative approach for patients with atrial fibrillation of more than 2 days in duration is transesophageal echocardiography and cardioversion if no thrombus is found, followed by anticoagulation for 3 to 4 weeks.

For prevention of stroke, warfarin therapy should be used in patients who have other risk factors for stroke. Risk of thromboembolism can be determined using the CHA$_2$DS$_2$-VASc score (Table 3.4), and anticoagulation is considered with 1 risk factor and is indicated (unless there is an important contraindication) when the CHA$_2$DS$_2$-VASc score is 2 or more. For patients in whom warfarin therapy is indicated, the international normalized ratio should be maintained in the range of 2.0 to 3.0. Anticoagulation decreases the incidence of thromboembolism by close to 70% in this population.

KEY FACTS

- ✓ Identification of atrial flutter on ECG—characteristic sawtooth pattern of atrial activity (rate, 240–320 bpm)
- ✓ Atrial fibrillation—most common arrhythmia
- ✓ Prevalence of atrial fibrillation—increases with age; affects 5% of patients age ≥65 years
- ✓ Conditions associated with atrial fibrillation—hypertension, cardiomyopathy, valvular heart disease, sleep-disordered breathing, sick sinus syndrome, WPW syndrome, alcohol use, thyrotoxicosis
- ✓ Initial management of atrial fibrillation—rate control with AV blocking agents and assessment of stroke risk and need for anticoagulation

Table 3.4 • The 2009 Birmingham Schema Expressed as a Point-Based Scoring System, With the Acronym CHA_2DS_2-VASc

Risk Factor	Score
Congestive heart failure/left ventricular dysfunction	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke/transient ischemic attack/thromboembolism	2
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
Age 65-74 years	1
Sex **c**ategory (ie, female gender)	1

From Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. Chest. 2010 Feb;137(2):263-72; used with permission.

Other Supraventricular Tachycardias

Tachycardia (rate >100 bpm) is characterized as a narrow complex or a wide complex tachycardia.

Paroxysmal Supraventricular Tachycardia

Paroxysmal supraventricular tachycardia (PSVT) is due to a reentrant mechanism with an abrupt onset and termination, a regular rate, and a narrow QRS complex (Figure 3.9), unless there is a rate-related or preexisting bundle branch block. Acutely, PSVT responds to vagal maneuvers; adenosine (or verapamil or diltiazem if PSVT is recurrent) terminates the arrhythmia in 90% of patients. PSVT generally is not a life-threatening arrhythmia; it often occurs in an otherwise normal heart. The preferred method for management of symptomatic PSVT is catheter ablation, which has success rates of more than 90%. For patients in whom catheter ablation is not feasible or preferred, β-blockers or calcium channel blockers may be useful.

Multifocal atrial tachycardia is an automatic atrial rhythm diagnosed when 3 or more distinct atrial foci (P waves of different morphologic forms) are present and the rate exceeds 100 bpm (Figure 3.10). This rhythm occurs primarily in patients with decompensated lung disease and associated hypoxia, increased catecholamines (exogenous and endogenous), atrial stretch, and local tissue acid-base and electrolyte disturbances. Digoxin worsens multifocal atrial tachycardia (shortens atrial refractoriness). Multifocal atrial tachycardia is best treated with calcium channel blockers and correction of the underlying medical illnesses, including increasing oxygenation.

Differentiating Supraventricular Tachycardia With Aberrancy From Ventricular Tachycardia

Wide QRS tachycardia may be due to supraventricular tachycardia with aberrancy or to ventricular tachycardia (Figure 3.11). Findings useful for identifying ventricular tachycardia are listed in Box 3.3.

Wide QRS tachycardias are ventricular in origin in more than 85% of cases and are often well tolerated. The absence of hemodynamic compromise during tachycardia does not prove the tachycardia is supraventricular in origin.

A simple approach to a wide complex tachycardia is to review the morphologic features of the complex in lead V_1 and decide whether the pattern is that of right or left bundle branch block. If the morphologic pattern exactly matches a normal right or left bundle branch block, then it might be supraventricular with rate-related aberrant conduction. The safest approach to any wide complex tachycardia is to assume that it is due to ventricular tachycardia and to treat it accordingly.

WPW Syndrome

WPW syndrome is defined as symptomatic tachycardia occurring in a patient with evidence of anterograde accessory pathway conduction during sinus rhythm on the surface ECG (the WPW pattern). WPW pattern is characterized by a short PR interval (<0.12 second), a delta wave, and a prolonged QRS interval (>0.12 second) resulting from preexcitation of the ventricle by conduction across an accessory pathway. However, not all patients with preexcitation have a short PR interval. Normal PR conduction may occur if the accessory pathway is distant from the AV node (as can be the case with a left lateral pathway).

Key Definition

Wolff-Parkinson-White syndrome: *symptomatic tachycardia occurring in a patient with evidence of anterograde accessory pathway conduction during sinus rhythm on surface electrocardiography.*

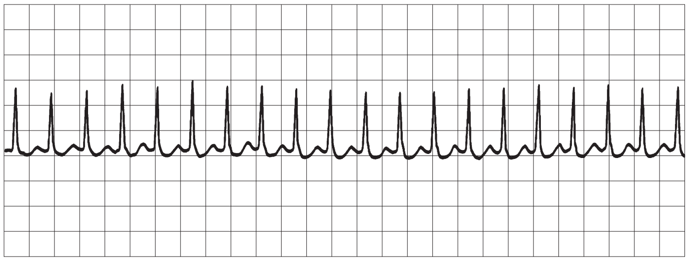

Figure 3.9. *Paroxysmal Supraventricular Tachycardia.*

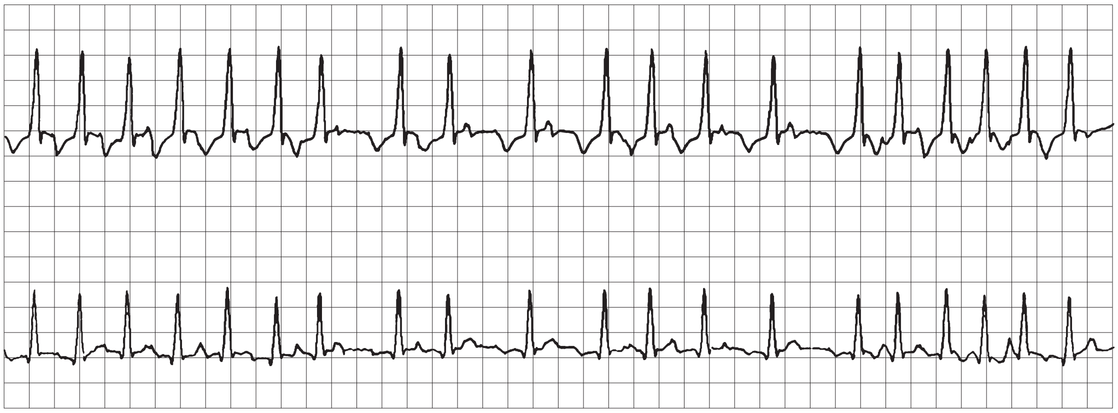

Figure 3.10. Multifocal Atrial Tachycardia. Simultaneous recordings show 3 or more P waves of different morphologic patterns.
(Lower tracing, adapted from MKSAP IX: Part C, Book 1, c1992. American College of Physicians; used with permission.)

Preexcitation occurs in about 2 of 1,000 patients; tachycardia subsequently develops in 70%. The most serious rhythm disturbance is atrial fibrillation with rapid ventricular conduction over the accessory pathway leading to ventricular fibrillation (Figure 3.12). Patients who are asymptomatic have a negligible chance of sudden death. For patients who are symptomatic, the incidence of sudden death is 0.0025 per patient-year.

The tachycardia in WPW syndrome can occur with a circuit that travels down the AV node and then back to the atrium via the accessory pathway (orthodromic; most common circuit and results in a narrow complex tachycardia)

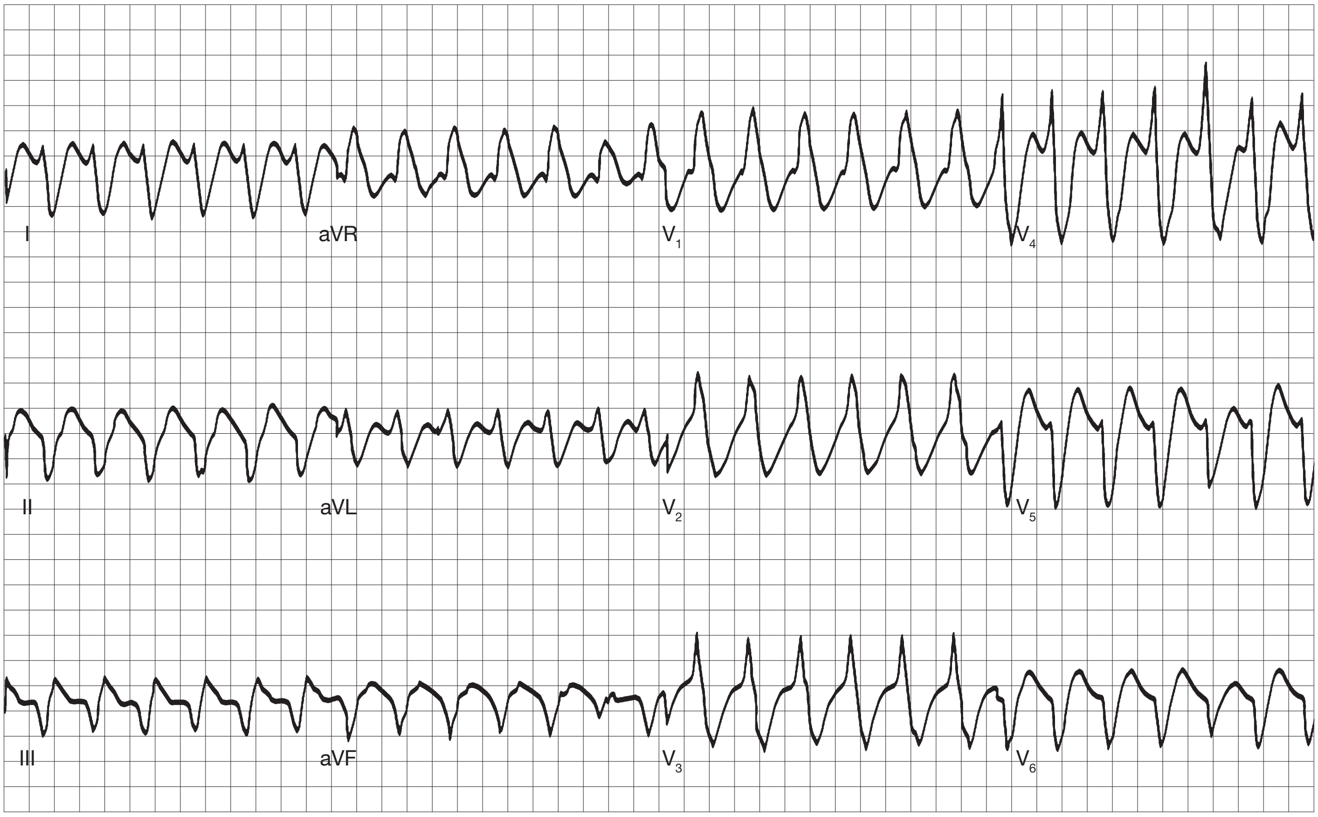

Figure 3.11. Ventricular Tachycardia With a Wide QRS Complex, Northwest Axis, and Fusion Complexes. Patient had normal blood pressure.

Box 3.3 • Findings That Differentiate Ventricular Tachycardia From Supraventricular Tachycardia With Aberrancy

- Evidence of AV dissociation with P waves “marching through” the QRS complexes
- A QRS width >0.14 second if the tachycardia has a right BBB pattern and >0.16 second if the tachycardia has a left BBB pattern
- Northwest axis (axis between −90° and −180°)
- A different QRS morphologic pattern in patients with a preexisting BBB
- A history of structural heart disease

Abbreviations: AV, atrioventricular; BBB, bundle branch block.

(Figure 3.13). It can also occur with a circuit that travels down the accessory pathway and then back up the AV node (antidromic; results in a wide complex tachycardia) (Figure 3.14).

EP testing and radiofrequency ablation of the accessory pathway are indicated in patients with symptomatic WPW syndrome.

WPW syndrome is associated with an increased frequency of atrial fibrillation related to the presence of the accessory pathway (Figure 3.12). After successful catheter ablation of the accessory pathway, atrial fibrillation resolves in most cases. During “preexcited” atrial fibrillation, wide, irregular, and rapid ventricular complexes are seen because activation down the accessory pathway does not use the normal His-Purkinje system (Figure 3.15). In preexcited atrial fibrillation, the drug of first choice is procainamide, which slows the accessory pathway and intra-atrial conduction and may convert the atrial fibrillation to sinus rhythm. Acute administration of digoxin, adenosine, β-blockers, or calcium channel blockers in patients who present with atrial fibrillation and WPW syndrome is contraindicated because of the risk of ventricular fibrillation. If the heart rate is rapid and there is hemodynamic compromise, cardioversion should be performed.

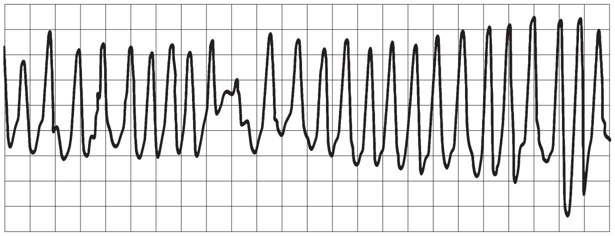

Figure 3.12. *Atrial Fibrillation in Wolff-Parkinson-White Syndrome. Recording shows a wide QRS complex and irregular RR intervals.*

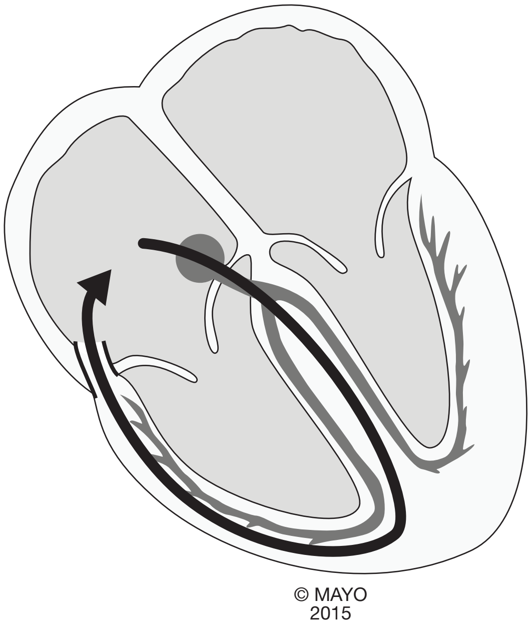

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Figure 3.13. *Typical Mechanism of Supraventricular Tachycardia in Wolff-Parkinson-White Syndrome (Orthodromic Atrioventricular Reentry). Result is a narrow QRS complex because ventricular activation is over the normal conduction system.*

Narrow complex tachycardias that involve the AV node in the circuit (ie, atrioventricular node reentry tachycardia and orthodromic or antidromic atrioventricular reentry tachycardia) are often terminated with vagal maneuvers or

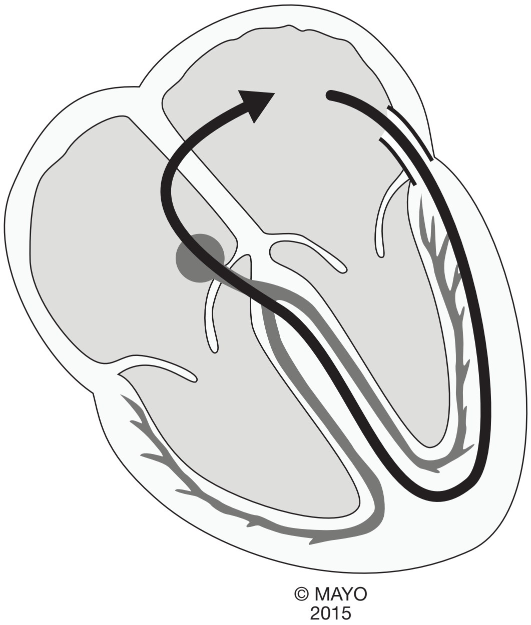

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Figure 3.14. *Unusual Mechanism of Supraventricular Tachycardia in Wolff-Parkinson-White Syndrome. Result is a wide QRS complex because ventricular activation is over an accessory pathway. This arrhythmia is difficult to distinguish from ventricular tachycardia.*

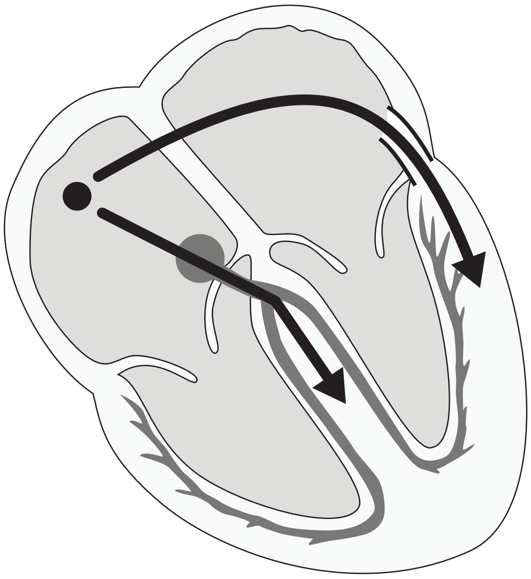

Figure 3.15. *Conduction of Sinus Impulses in Wolff-Parkinson-White Syndrome. Ventricles are activated over the normal atrioventricular node–His-Purkinje system and accessory pathway. Result is a fusion complex (QRS and delta wave).*

intravenously administered adenosine or verapamil because the circuit is interrupted at the AV node. Recurrence can be prevented with a β-blocker or a calcium antagonist. Other antiarrhythmic medications are rarely used. Radiofrequency ablation is used to cure tachycardia and should be strongly considered for symptomatic patients.

Ventricular Ectopy and Nonsustained Ventricular Tachycardia

Management of frequent ventricular ectopy and nonsustained ventricular tachycardia is based on the underlying cardiac lesion. In symptomatic patients, management includes β-blockers or calcium channel blockers for symptom control and, in rare cases of frequent monomorphic symptomatic ventricular ectopy, catheter ablation. Patients with a structurally normal heart and complex ectopy or nonsustained ventricular tachycardia have an excellent prognosis. Management includes reassurance or, if bothersome symptoms persist, calcium channel blockers, β-blockers, or ablation.

Ventricular Tachycardia and Fibrillation

Survivors of sudden cardiac death have a risk of death approaching 30% in the first year after hospital dismissal. Antiarrhythmic drug therapy has not been shown to have benefit. ICD therapy, however, improves survival outcomes.

Torsades de Pointes

Torsades de pointes is a form of polymorphic ventricular tachycardia with a characteristic morphologic pattern described as a “twisting of the points” (Figure 3.16).

Torsades de pointes occurs in the clinical setting of QT interval prolongation. Common causes include medications that prolong the QT interval (eg, quinidine, procainamide, dofetilide, sotalol), electrolyte disturbance (hypokalemia), and bradycardia (especially after myocardial infarction). Acute treatment options include isoproterenol infusion (to increase heart rate and shorten QT interval), temporary overdrive pacing (if due to bradycardia), and correction of electrolyte abnormalities. QT interval prolongation may be due to an inherited disorder of cardiac ion channels such as the long QT syndrome. Patients with this abnormality require evaluation and, in some cases, implantation of a cardioverter-defibrillator.

Tachycardia-Mediated Cardiomyopathy

Persistent tachycardia (usually due to poorly controlled atrial fibrillation) may lead to progressive ventricular dysfunction (termed *tachycardia-mediated cardiomyopathy*). It is reversible in most cases because control of the ventricular rate improves ventricular function.

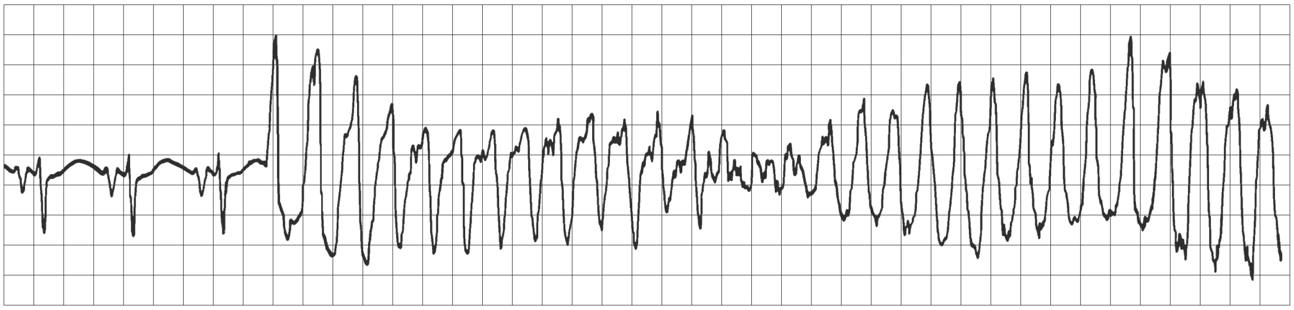

Figure 3.16. *Torsades de Pointes in a Patient With Long QT Syndrome.*

(Adapted from Hammill SC. Electrocardiographic diagnoses: criteria and definitions of abnormalities. In: Murphy JG, Lloyd MA, editors. Mayo Clinic Cardiology: Concise Textbook. 4th ed. Rochester [MN]: Mayo Clinic Scientific Press and New York [NY]: Oxford University Press; c2013. p. 205-38; used with permission of Mayo Foundation for Medical Education and Research.)

Ventricular Arrhythmias During Acute Myocardial Infarction

Asymptomatic complex ventricular ectopy, including nonsustained ventricular tachycardia, should not be treated empirically with antiarrhythmic medications in the acute phase because the risk of proarrhythmia outweighs the potential benefit of therapy for reducing the incidence of sudden cardiac death after hospital dismissal. Ventricular tachycardia and fibrillation occurring within 24 hours after myocardial infarction are independent risk factors for in-hospital death but not for subsequent total mortality rate or death due to an arrhythmic event after hospital dismissal and do not require antiarrhythmic or ICD therapy. Ventricular tachycardia and fibrillation occurring more than 24 hours after an acute myocardial infarction (without ongoing ischemia or reinfarction) are independent risk factors for increased total mortality rate and death due to an arrhythmic event after hospital dismissal. Patients may be assessed with EP testing; treatment is usually with an ICD. Routine use of a prophylactic ICD after myocardial infarction is not supported by available data. Refractory ventricular tachycardia and fibrillation during acute myocardial infarction should be treated with intravenously administered lidocaine or amiodarone.

Role of Pacing in Acute Myocardial Infarction

Among patients with an acute inferior myocardial infarction, 5% to 10% have Mobitz I second-degree or third-degree block in the absence of bundle branch block. This finding usually is transient, tends not to recur, and usually does not require pacing. Patients in whom transient complete heart block develops in association with a bundle branch block are at risk for recurrent complete heart block and should undergo permanent pacing. A new bundle branch block that never progresses to complete heart block is not an indication for permanent pacing, however. Second-degree (Mobitz II) block with bilateral bundle branch block and third-degree (complete) AV block warrant pacing.

Syncope

Syncope is defined as a transient loss of consciousness with spontaneous recovery. It can be categorized as cardiogenic (about 30% of cases are due to bradycardia or tachycardia) or noncardiogenic (neurologic, metabolic, or psychiatric) (Box 3.4).

Key Definition

Syncope: *transient loss of consciousness with spontaneous recovery.*

KEY FACTS

- ✓ Multifocal tachycardia—best treated with calcium channel blockers and correction of underlying medical illnesses
- ✓ Wide QRS tachycardias—ventricular in origin in ≥85% of cases and are well tolerated
- ✓ Safest approach to wide complex tachycardia—assume it is due to ventricular tachycardia and treat accordingly
- ✓ Persistent tachycardia—may lead to progressive ventricular dysfunction; is reversible in most cases because control of ventricular rate improves ventricular function
- ✓ During and after myocardial infarction—prevention of myocardial ischemia and use of β-blockers are essential
- ✓ Syncope—can be categorized as cardiogenic (~30% of cases are due to bradycardia or tachycardia) or noncardiogenic (neurologic, metabolic, or psychiatric)

Box 3.4 • Major Causes of Syncope

- Cardiogenic
  - Cardiogenic syncope
  - Structural heart disease
  - Coronary artery disease
  - Rhythm disturbances
- Reflex syncope
  - Vasovagal
  - Carotid sinus hypersensitivity
  - Situational
    - Micturition
    - Deglutition
    - Defecation
    - Glossopharyngeal neuralgia
    - Postprandial
    - Tussive
    - Valsalva maneuver
    - Oculovagal
    - Sneeze
    - Instrumentation
    - Diving
    - After exercise
- Orthostatic hypotension
- Noncardiogenic
  - Neurologic
  - Metabolic
  - Psychiatric

Data from Wieling W, Shen W-K. Syncope: approach to management. In: Low PA, Benarroch EE, editors. Clinical autonomic disorders. 3rd ed. Philadelphia (PA): Lippincott Williams & Wilkins; c2008. p. 493-514.

Box 3.5 • Risk Stratification in Patients With Unexplained Syncope[a]

High-Risk Factors

- Coronary artery disease, previous myocardial infarction
- Structural heart disease
- Left ventricular dysfunction
- Congestive heart failure
- Older age
- Abrupt onset
- Serious injuries
- Abnormal ECG (presence of Q wave, bundle branch block, or atrial fibrillation)

Low-Risk Factors

- Isolated syncope without underlying cardiovascular disease
- Younger age
- Symptoms consistent with a vasovagal cause
- Normal ECG

Abbreviation: ECG, electrocardiography.

[a] In patients who present with a prodrome (eg, nausea, diaphoresis), a neurocardiogenic mechanism is likely. Patients who have rapid recovery (less than 5 to 10 minutes) rarely have a neurologic cause for syncope and are most likely to have syncope due to seizure or "brain hypoperfusion" because recovery in such circumstances takes hours. Thus, for cases in which recovery from syncope is rapid and no residual neurologic signs or symptoms are present, detailed (and expensive) neurologic evaluation should be avoided.

Data from Wieling W, Shen W-K. Syncope: approach to management. In: Low PA, Benarroch EE, editors. Clinical autonomic disorders. 3rd ed. Philadelphia (PA): Lippincott Williams & Wilkins; c2008. p. 493-514.

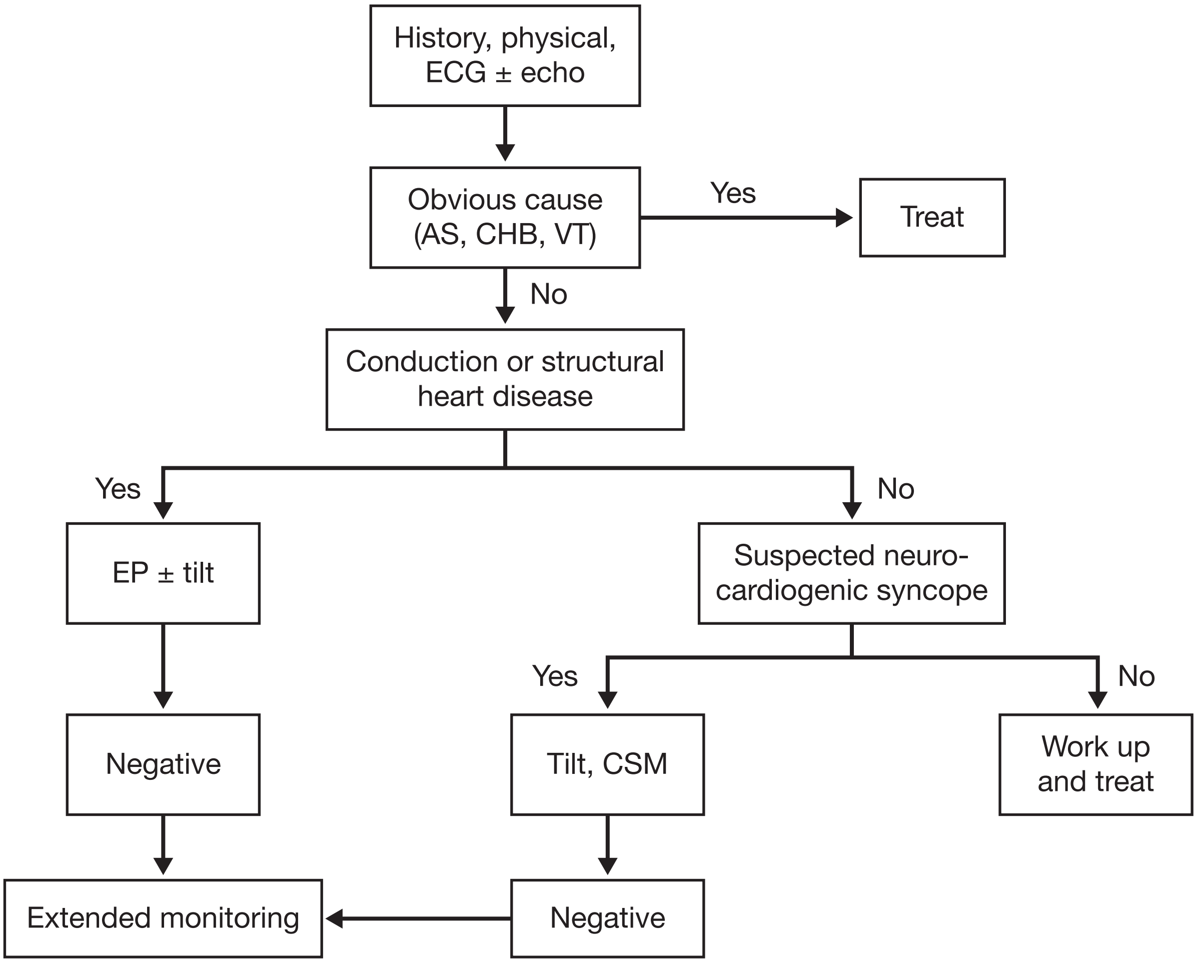
History, physical, ECG ± echo
Obvious cause (AS, CHB, VT)
Yes
Treat
No
Conduction or structural heart disease
Yes
No
EP ± tilt
Suspected neuro-cardiogenic syncope
Yes
No
Negative
Tilt, CSM
Work up and treat
Extended monitoring
Negative

Figure 3.17. *Diagnostic Pathway for Evaluation of Syncope. AS indicates aortic stenosis; CHB, complete heart block; CSM, carotid sinus massage; ECG, electrocardiography; echo, echocardiography; EP, electrophysiologic study; tilt, tilt-table testing; VT, ventricular tachycardia.*

Evaluation of Syncope

The history and physical examination are highly valuable for the evaluation of syncope. Risk factors for a cardiogenic cause of syncope are listed in Box 3.5. Recommendations for evaluation of patients with syncope are outlined in Figure 3.17. Clinicians should consider EP testing in patients at increased risk for cardiogenic syncope. EP testing is usually not indicated if an arrhythmogenic cause (bradycardia or tachycardia) of syncope has been established unless other arrhythmias are suspected. A noninvasive approach should be considered in patients at low risk for cardiogenic syncope. Tilt-table testing can confirm the diagnosis in suspected vasovagal syncope. Tilt-table testing is not usually indicated after a single episode of syncope without injury or in cases with obvious vasovagal clinical features.

Management of Syncope

Pacemaker therapy is appropriate for sinus node dysfunction and advanced AV conduction disease. Management of recurrent neurocardiogenic syncope (vasovagal syncope) includes education about the mechanism and triggering factors, instruction regarding appropriate action (eg, sitting or lying down to avert episodes), instruction regarding maintenance of increased intravascular volume, and instruction on maneuvers to prevent venous pooling. Midodrine, which promotes increased venous return, may be considered. β-Blockers have limited or no benefit. Pacemaker therapy has a limited role in preventing vasovagal syncope when a pure cardioinhibitory response is documented.

4

Cardiac Manifestations of Systemic Diseases and Pregnancy[a]

LORI A. BLAUWET, MD; REKHA MANKAD, MD; SABRINA D. PHILLIPS, MD; KYLE W. KLARICH, MD

The Heart and Systemic Disease

Hyperthyroidism

Effects

Cardiovascular manifestations of hyperthyroidism include increased heart rate, stroke volume, and cardiac output. Peripheral vascular resistance is decreased, and thus pulse pressure is widened. As a result, myocardial oxygen consumption increases, which may precipitate angina. Other symptoms include palpitations, presyncope or syncope, and exertional dyspnea. Arrhythmias may occur.

Clinical Features

Common symptoms include weight loss, weakness (especially for elderly persons), and tachycardia or palpitations.

Common physical findings are tachycardia and a bounding pulse with a wide pulse pressure, a forceful apical impulse, and a systolic ejection murmur due to increased flow. Supraventricular tachycardia and atrial fibrillation are the most common arrhythmias. Angina may occur. Atrial fibrillation occurs in 10% to 20% of patients. Indeed, thyrotoxicosis should be excluded in patients with atrial fibrillation. Sinus rhythm is often restored spontaneously when a euthyroid state is achieved. Examination may also show tremor, and a goiter may be present.

Treatment

Treatment of hyperthyroidism usually leads to reversal of cardiac symptoms. If atrial fibrillation is present, the risk of embolization is high and anticoagulation should be considered. Cardioversion should not be attempted until a euthyroid state is achieved.

Hypothyroidism

Effects

Mucoprotein infiltration of the myocardium due to hypothyroidism can lead to cardiac enlargement and decreased systolic function. Hypothyroidism decreases metabolic rate and circulatory demand and can cause bradycardia, decreased contractility and stroke volume, and increased peripheral resistance. The cardiomyopathy is reversible if detected early and treated effectively. Hypothyroidism is associated with increased cholesterol levels (particularly an elevation in high-density lipoprotein level) and atherosclerosis.

KEY FACTS

- ✓ Atrial fibrillation—occurs in 10% to 20% of persons
- ✓ Mucoprotein infiltration of myocardium due to hypothyroidism—can lead to cardiac enlargement and decreased systolic function
- ✓ Hypothyroidism—associated with increased cholesterol levels (particularly high-density lipoprotein level) and atherosclerosis

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[a] Portions of this chapter have been previously published in Muchtar E, Blauwet LA, Gertz MA. Restrictive Cardiomyopathy: Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy. Circ Res. 2017 Sep 15;121(7):819-37; used with permission.

Symptoms

Patients may present with depression, lethargy, and slowed mentation. Hair loss on the scalp and lateral aspect of the eyebrows and a thick tongue may occur. Many patients report constipation and weight gain.

Physical Examination

Cardiac enlargement can be caused by myocardial disease or a pericardial effusion. The pulse volume is decreased as a result of reduced contractility. Sinus bradycardia usually is present. Other findings may include macroglossia, thinning or loss of the lateral third of the eyebrows, coarse hair and dry skin, and myxedema. Chest radiography shows increased cardiac size. Electrocardiography (ECG) shows low voltage of QRS with prolonged intervals of QRS, PR, and QT. If a large pericardial effusion is present, then in addition to low-voltage QRS, electrical alternans may be seen.

Treatment

Reversal of cardiac involvement occurs with early treatment of hypothyroidism.

Diabetes Mellitus

Effects

Diabetes mellitus is associated with premature atherosclerosis, which is twice as prevalent in diabetic men and 3 times more prevalent in diabetic women than in a nondiabetic population. Patients with diabetes have a higher prevalence of hypertension and hyperlipidemia. Angina and myocardial infarction manifest with nonclassic symptoms, or patients may have silent ischemia. Congestive heart failure may be the first manifestation of coronary artery disease among diabetic persons. Cardiomyopathy not associated with epicardial coronary atherosclerosis may also exist; this may be caused by small-vessel disease. Fatal myocardial infarction is more common in patients with diabetes than those who do not have diabetes.

Treatment

Aggressive management of traditional risk factors for coronary artery disease lowers mortality risk. Diabetes-specific risk factors for coronary artery disease may include poor glycemic control and urinary protein excretion. However, strict blood glucose control has come into question in recent years. The use of antihypertensive agents for aggressive lowering of blood pressure (systolic pressure ≤120 mm Hg, diastolic pressure ≤80 mm Hg) reduces mortality risk. Statins are effective for primary and secondary prevention of coronary artery disease in patients with both diabetes mellitus and age between 40 and 75 years (Circulation. 2014 Jun 24;129[25 Suppl 2]:S1-45). Angiotensin-converting enzyme inhibitors reduce cardiovascular events and death among patients with diabetes who are older than 55 years and have additional risk factors. To date, glycemic control has not been shown to lower the incidence of cardiovascular events.

Amyloidosis

Effects

Amyloidosis leads to extracellular deposition of insoluble proteins in organs and is classified by the precursor plasma proteins that form the extracellular fibril deposits. The primary systemic amyloidosis, also known as *AL amyloid*, is due to monoclonal immunoglobulin free light chains. Transthyretin (TTR) amyloid is either the hereditary (familial) type due to mutant TTR deposition and with autosomal dominant inheritance or the wild-type TTR type (previously referred to as *senile type*) due to abnormal deposition of wild-type TTR. Although nearly 30 different proteins may cause amyloid, the main two are amyloid due to AL amyloid and TTR. The other rare causes are identified when proper diagnostic strategy and accurate tissue typing are used. The heart is frequently involved, especially by AL amyloid; nearly 90% of patients with primary amyloidosis have clinical manifestations of cardiac dysfunction.

Cardiomyopathy results from protein infiltration, which causes thickened ventricular myocardium. Amyloid deposition in the atrioventricular cardiac valves may occur. Amyloid can also deposit in small vessels and lead to ischemia.

Cardiac involvement may occur in secondary amyloidosis, but it is usually not a prominent feature. Secondary amyloidosis occurs in association with chronic diseases, such as rheumatoid arthritis, tuberculosis, chronic infection, neoplasm (especially multiple myeloma), and chronic renal failure. In wild-type TTR amyloidosis, the heart is the most commonly involved organ, and prevalence increases after age 60 years.

Clinical Features

A high index of suspicion is necessary to identify cardiac amyloidosis early, and early diagnosis provides the only hope of a cure. Cardiac amyloid may cause congestive heart failure, arrhythmias, sudden death, angina, chest pain, pericardial effusion (usually not hemodynamically significant), and regurgitant murmurs. The natural history is usually intractable because of ventricular failure. Diastolic abnormalities are common and are the earliest manifestation in the disease process. Although cardiac amyloidosis has been classified as a *restrictive cardiomyopathy*, any abnormality of diastolic dysfunction can signal early amyloid infiltration. Restrictive physiologic factors (grade 3-4 diastolic dysfunction) indicate a poor prognosis. Newer imaging techniques have been helpful in identifying the disease, including strain echocardiography and cardiac magnetic resonance imaging (MRI), and, if TTR amyloid, technetium Tc 99m–labeled pyrophosphate (PYP).

Amyloidosis should be considered when a patient (usually age >30-70 years) presents with dyspnea and progressive edema of the lower extremities. Atrial fibrillation is common among these patients. Associated conditions such as vocal hoarseness, carpal tunnel syndrome, or peripheral neuropathy may be present and point to the systemic nature of the disease. A key finding is a low-voltage (or even normal voltage in up to 25% of cases) QRS complex with or without other conduction abnormalities (eg, increased PR interval, bundle branch block) coupled with echocardiographic findings of thick walls and, usually, preserved left ventricular ejection fraction.

Diagnosis

Cardiac involvement is suggested by the classic ECG finding of a low-voltage QRS complex. However, this is a nonspecific finding, and 20% to 25% of patients with cardiac amyloid may have normal ECG findings. Echocardiography is particularly useful, showing increased left ventricular wall thickness, in contradistinction to the small (or normal) voltage on ECG (Figure 4.1). The atria generally are dilated. The cardiac valves may show some thickening and regurgitation. A small pericardial effusion may be present. Diastolic function generally is abnormal; in the early stages of the disease, findings consistent with prolonged relaxation are found, whereas restrictive filling (consistent with high left ventricular filling pressures) is found in later stages. All patients with clinically suspected cardiac amyloid and a supporting echocardiogram should undergo blood testing for serum free light chains, serum and urine electrophoresis with immunofixation, and a subcutaneous fat aspirate. The fat aspirate is positive in 90% of AL and 15% of TTR amyloid cases. Cardiac MRI showing findings consistent with amyloid can be helpful. When MRI and echocardiography are positive but the electrophoresis and biopsy are negative, a technetium Tc 99m–labeled PYP can lead to the diagnosis of TTR amyloid. Ultimately, when clinical suspicion is high and less invasive testing is negative, a cardiac biopsy may still be essential.

KEY FACTS

- ✓ Cardiomyopathy—due to protein infiltration and the resulting thickened ventricular myocardium
- ✓ Cardiac amyloidosis—classified as restrictive cardiomyopathy, yet any abnormality from diastolic dysfunction can signal early amyloid infiltration
- ✓ Cardiac involvement—suggested by the classic ECG finding of a low-voltage QRS complex

Treatment

Although cardiac amyloidosis has a generally poor prognosis, early diagnosis is essential. It is important to have patients referred to centers experienced in typing the amyloid because, depending on the type, successful established and emerging therapies are available. Referral to a tertiary center with expertise in amyloidosis is warranted because prior experimental protocols have evolved into treatment options, such as stem cell transplant and chemotherapy in primary amyloidosis, liver transplant in familial amyloidosis, and emerging therapies in wild-type (senile) amyloidosis.

Cardiac Sarcoidosis

Effects

Sarcoidosis is a multisystem inflammatory disorder of unknown cause characterized by the presence of noncaseating

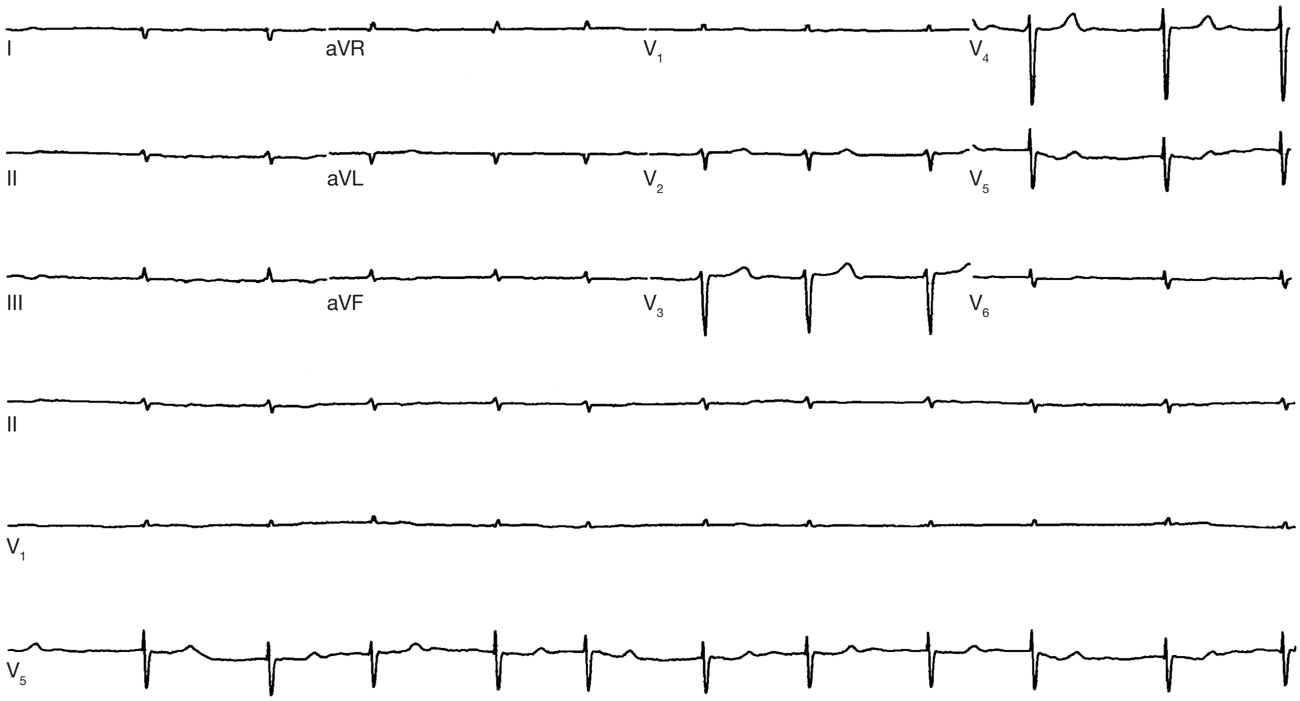

Figure 4.1. *Electrocardiography in Cardiac Amyloidosis. Classic finding is low-voltage complexes.*

granulomatous inflammation. It frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltrates, uveitis, or skin lesions, or a combination. The heart, liver, spleen, nervous system, bone marrow, kidneys, bones, joints, muscles, and other organs may also be involved. Sarcoidosis commonly affects young and middle-aged adults, but children and elderly persons may also be affected.

Only a small proportion of patients with sarcoidosis receive the diagnosis of cardiac involvement, likely because the diagnosis is often missed. According to 2 autopsy series of patients with systemic sarcoidosis, the prevalence of cardiac involvement is approximately 25%. Isolated cardiac sarcoidosis occurs, albeit rarely.

Clinical Features

Asymptomatic cardiac involvement is common. Among patients with symptomatic cardiac involvement, clinical signs and symptoms tend to differ according to the extent and location of granulomatous inflammation and fibrosis. Granulomas most frequently infiltrate the left ventricular myocardium, but any area of the heart—including the right ventricle, atria, papillary muscles, valves, pericardium, and coronary arteries—may be involved. The most common presentation is heart failure, although patients may present with syncope, palpitations, dyspnea, fatigue, chest pain, or sudden cardiac death.

Cardiac involvement may precede, occur concurrently, or follow lung or other organ involvement. Thus, clinicians should consider the possibility of cardiac sarcoidosis in patients with known extracardiac sarcoidosis who have cardiac symptoms, ECG changes, or abnormal findings on cardiac imaging. The diagnosis of cardiac sarcoidosis also should be considered in otherwise healthy young or middle-aged persons who present with cardiac symptoms, high-grade heart block, arrhythmias, or heart failure without a preceding diagnosis of extracardiac sarcoidosis.

Diagnosis

The most commonly used criteria for diagnosing cardiac sarcoidosis are the Japanese Ministry of Health and Welfare criteria and the Heart Rhythm Society expert consensus statement. Both sets of diagnostic criteria list 2 pathways to diagnosis: a histologic pathway and a clinical pathway. The gold standard for confirmation of the diagnosis of cardiac sarcoidosis is a positive endomyocardial biopsy. Because of the patchy nature of granulomatous involvement in the myocardium, however, the diagnostic yield of endomyocardial biopsy is only about 20%. Patients with extracardiac sarcoidosis can have the diagnosis of cardiac involvement in the absence of an endomyocardial biopsy when certain clinical criteria are met. These criteria include advanced heart block, ventricular tachycardia, and decreased left ventricular ejection fraction with no other known etiologic involvement. Cardiac MRI and cardiac positron emission tomography are both increasingly used to aid in the diagnosis of cardiac sarcoidosis because of the ability of these advanced imaging modalities to detect myocardial inflammation and fibrosis.

Treatment

Corticosteroids are the mainstay treatment of patients with cardiac sarcoidosis, although a paucity of data supports the effectiveness of this therapy. No clear guidelines are available regarding when to initiate corticosteroid therapy. Most experts agree that immunosuppression should be considered for symptomatic patients with evidence of active myocardial inflammation and any of the following criteria: 1) reduced left ventricular ejection fraction, 2) high-grade AV block, 3) frequent premature ventricular contractions or frequent nonsustained ventricular tachycardia, or 4) sustained ventricular tachycardia or ventricular fibrillation. It is uncertain whether asymptomatic patients should be treated. Corticosteroid-sparing agents are often used for refractory cases or when patients have adverse effects from corticosteroid therapy. Antimetabolites, such as methotrexate, azathioprine, leflunomide, mycophenolate mofetil, and cyclophosphamide, have been used as second-line agents. If the disease progresses despite use of glucocorticoids or a second-line agent, or both, tumor necrosis factor-α inhibition with either infliximab or adalimumab should be considered.

Ventricular tachyarrhythmias are common for patients with cardiac sarcoidosis. Amiodarone is often prescribed in the acute setting, but long-term use typically is avoided because of potential lung toxicity. Catheter radiofrequency ablation may be useful for some patients with frequent premature ventricular contractions or ventricular tachycardia.

Because many patients who have cardiac sarcoidosis present with high-grade AV block, pacemaker implantation is frequently indicated. Implantable cardioverter-defibrillator placement is indicated for patients with history of spontaneous sustained ventricular arrhythmias or with a left ventricular ejection fraction of 35% or less despite optimal medical therapy and a period of immunosuppression when inflammation is present. Implantable cardioverter-defibrillator placement may also be considered for patients who have cardiac sarcoidosis with unexplained syncope or near syncope and inducible sustained ventricular arrhythmias.

Heart transplant is occasionally indicated for patients with cardiac sarcoidosis who have intractable arrhythmias or end-stage heart failure. Rarely, sarcoidosis may recur in the transplanted heart, particularly for patients receiving no or low-dose corticosteroid treatment.

Hemochromatosis

Effects

Hemochromatosis, an iron-storage disease, may be primary or secondary (related to exogenous iron, usually from repeated transfusions). Iron may deposit within the cardiac cells. Cardiac hemochromatosis is usually accompanied by other organ involvement—primarily pancreas, liver, and skin—leading to the classic tetrad of diabetes mellitus, liver disease, brown skin pigmentation, and congestive heart failure. Affected patients may present with cardiomegaly, congestive heart failure (with features of systolic and diastolic dysfunction), and arrhythmias.

Clinical Features

Many patients are asymptomatic or have minimal symptoms. Often, the earliest manifestations are fatigue, hair loss, arthralgia, palpitations and syncope, impotence or loss of libido, and amenorrhea. Clinically, patients may present with new-onset diabetes mellitus or glucose intolerance. Symptoms and signs of heart failure may be present. Patients often present with arrhythmias (both supraventricular and ventricular), or may even have sudden cardiac death or out-of-hospital cardiac arrest. A clinical clue is the discovery of a dilated heart with reduced function in a patient who presents with cardiac arrest and no evidence of coronary artery disease. In such a case, hemochromatosis diagnosis should be entertained.

Diagnosis

The 2 key tests for hemochromatosis are serum transferrin saturation and serum ferritin. Transferrin saturation values that exceed 45% are considered too high. Increased serum ferritin values establish the diagnosis of hemochromatosis. Liver function tests can help identify liver damage that may be coexistent in hemochromatosis. Cardiac MRI has been established as a fast and noninvasive way to measure the degree of iron overload in the heart and other organs. Genetic testing for this autosomal recessive genetic disorder is indicated when it is suspected from the results of clinical testing. A liver biopsy may be indicated for patients with evidence of cirrhosis.

Treatment

After clinical cardiac symptoms appear, the prognosis is poor unless treatment is initiated with a combination of phlebotomy and iron chelation.

KEY FACTS

- ✓ Cardiac manifestations of hyperthyroidism—increased heart rate, stroke volume, and cardiac output
- ✓ Diabetes mellitus—associated with premature atherosclerosis
- ✓ Diabetes mellitus—prevalence of hypertension and hyperlipidemia is increased; angina and myocardial infarction manifest with nonclassic symptoms (or silent ischemia is present)
- ✓ Amyloidosis-associated cardiomyopathy—results from protein infiltration, which causes thickened ventricular myocardium; classic finding of cardiac involvement is low-voltage QRS complex on ECG
- ✓ Hemochromatosis—may be primary or secondary; iron may deposit within cardiac cells

Carcinoid Heart Disease

Effects

Liver or lung metastases from carcinoid tumors can produce a classic due to production of serotoninlike substances. These substances cause cutaneous flushing, wheezing, and diarrhea (the carcinoid syndrome) and are toxic to cardiac valves. Cardiac involvement occurs in approximately 50% of patients with hepatic or pulmonary metastasis; toxic effects generally affect right-sided cardiac valves. Left-sided valves can be affected when a cardiac shunt is present; the shunt allows right-to-left movement of the serotoninlike substances through the bloodstream. The left-sided involvement can also occur when the disease burden is high or in the presence of bronchial or gonadal carcinoid deposits. Carcinoid lesions are fibrous plaques that form on valvular endocardium. The valve leaflets become thickened, relatively immobile, and retracted. Regurgitation results, with some stenosis of the tricuspid and pulmonary valves.

Clinical Features

Patients may report weight loss, fatigue, watery diarrhea (>10 stools daily), dyspnea on exertion, and intermittent hot flashes. Typical findings on examination are an increased jugular venous pressure profile, a prominent *v* wave, cardiac murmur, a pulsatile liver that may be enlarged, ascites, and, usually, peripheral edema. Audible wheezes may be present, and patients may have a ruddy complexion.

Diagnosis

ECG typically shows right ventricular hypertrophy and right bundle branch block. The diagnosis is made with identification of a thickened tricuspid valve and pulmonary valve (and left-sided valves when a shunt is present). Lung and liver metastasis may be found when computed tomography is performed. The diagnosis is confirmed by a 24-hour urine measurement of 5-hydroxyindoleacetic acid. Acquired tricuspid and pulmonary stenosis with or without regurgitation is rare and should always raise the possibility of carcinoid heart disease.

Treatment

Treatment of the underlying tumor is important for symptom relief. In the clinical setting of right heart failure (eg, intractable edema, ascites, dyspnea), surgery may be warranted. Treatment of carcinoid syndrome may include octreotide and lanreotide, which may reduce the signs and symptoms of carcinoid syndrome, including skin flushing and diarrhea. Octreotide may also slow the growth of carcinoid tumors. Surgical therapies can include tricuspid valve replacement and pulmonary valve resection. Other treatments such as hepatic embolization and chemotherapy should be instituted in collaboration with oncology, radiology, and cardiology teams experienced in the treatment of this rare syndrome.

Hypereosinophilic Syndrome

Effects

This syndrome usually affects young (age 20-50 years) male patients. Causes include idiopathic hypereosinophilia known as **Löffler endocarditis**, reactive or allergic eosinophilia, leukemic or neoplastic eosinophilia, and Churg-Strauss syndrome. All of these may have cardiac manifestations.

Key Definition

Löffler endocarditis: *an uncommon restrictive cardiomyopathy resulting from eosinophil infiltration of the endocardium, leading to tissue damage and fibrosis.*

Clinical Features

Patients typically present with weight loss, fatigue, dyspnea, syncope, and systemic embolization. Pulmonary involvement should prompt consideration of Churg-Strauss syndrome. Cardiac manifestations include arrhythmias, myocarditis, conduction abnormalities, and thrombosis. Cardiac eosinophilic deposition may occur, and clots form in the ventricular apices and the inflow surfaces of the mitral and tricuspid valves. Matting down of the atrioventricular valves occurs, causing considerable regurgitation. Scarring develops where the clot formed, leading to endomyocardial fibrosis and a restrictive cardiomyopathy.

Diagnosis

The finding of persistent eosinophil concentrations of more than 1.5×10^9/L is typically associated with hypereosinophilia and end-organ damage.

Treatment

The treatment strategy should be aimed at the underlying cause of the increased eosinophil count. It may be due to primary disease of the bone marrow or systemic illness such as Churg-Strauss syndrome.

Systemic Lupus Erythematosus

Systemic lupus erythematosus may involve any of the cardiac structures. Cardiac involvement may include pericarditis with or without a pericardial effusion, characterized by a positive antinuclear antibody in the pericardial fluid, myocarditis (more common in patients with anti-Ro antibody), valvulopathy, and coronary arteritis. Pericarditis typically occurs during a lupus flare. **Libman-Sacks endocarditis** (nonbacterial thrombotic endocarditis), which results in noninfective vegetations, occurs in a large percentage of patients with systemic lupus erythematosus. Libman-Sacks endocarditis does not tend to correlate with lupus flares. These vegetations are more common with concomitant antiphospholipid antibody syndrome. The vegetations may embolize and, less frequently, interfere with valvular function. Lupus patients are also at higher risk of coronary atherosclerosis than matched controls. Congenital heart block may occur in newborns of mothers with lupus who have anti-La and anti-Ro antibodies due to myocarditis and to inflammation and fibrosis of the conduction system (neonatal lupus).

Key Definition

Libman-Sacks endocarditis: *A nonbacterial thrombotic endocarditis that results in noninfective vegetations, occurs in a large percentage of patients with systemic lupus erythematosus, and does not tend to correlate with lupus flares.*

Scleroderma

Cardiac involvement is manifested by intramural coronary involvement and immune-mediated endothelial injury, which is often associated with the Raynaud phenomenon clinically (due to peripheral small-vessel involvement). Other systemic features include sclerotic skin changes and esophageal abnormalities. Cardiac involvement is the third most common cause of death among patients with scleroderma, usually due to pulmonary hypertension and cor pulmonale. Conduction defects occur in up to 20% of patients. A pericardial effusion, which is usually clinically silent, is found in one-third of patients.

Rheumatoid Arthritis

Nearly all cardiac components, including pericardium, myocardium, valves, coronary arteries, and aorta, may be affected in patients with rheumatoid arthritis. Granulomatous inflammation and nongranulomatous inflammation of valve leaflets occur but rarely lead to severe valvular incompetence. Associated pericarditis is typically linked with a low glucose level and complement depletion in the pericardial fluid. Cardiac tamponade is rare, however. Rheumatoid nodules in the conduction system can lead to heart block. Aortitis and pulmonary hypertension due to pulmonary vasculitis are rare complications. Patients with rheumatoid arthritis have a higher risk of coronary artery disease and heart failure (specifically, heart failure with preserved ejection fraction) than patients without rheumatoid arthritis.

Ankylosing Spondylitis

Approximately 10% of patients with ankylosing spondylitis have aortic dilatation and aortic regurgitation. Aortic valve cusp distortion and retraction also may cause considerable aortic regurgitation. Fibrosis and inflammation of the conduction system may occur.

Marfan Syndrome

Degeneration of elastic tissues occurs in this autosomal dominant condition. Features include arachnodactyly, tall stature, pectus excavatum, kyphoscoliosis, and lenticular dislocation. Cardiac involvement is common, including mitral valve prolapse, aortic regurgitation due to aortic dilatation, and an increased risk of aortic dissection. Long-term β-adrenergic blockade decreases the rate of aortic dilatation and the risk of aortic dissection. Angiotensin receptor blockade is emerging as a treatment to prevent aortic dilatation and dissection. The dissection can occur at any aortic dimension, but risk increases with increasing aortic dimension. Currently, operative intervention for aortic replacement is indicated for aortic dimension more than 50 mm or for rapid aortic dilatation (>5 mm increase in dimension in 1 year).

Cardiac Trauma

Cardiac contusion may lead to arrhythmia, increased cardiac enzyme values, transient regional wall motion abnormalities, and pericardial effusion or tamponade. It may also cause disruption of the aorta or valves (tricuspid valve most often) or right ventricular rupture. Commotio cordis is sudden cardiac death due to trauma, characteristically mild trauma to the chest wall. This is generally due to a nonpenetrating blow (eg, by a baseball or softball) leading to instantaneous cardiac arrest. Cardiac disease is often absent. The trauma must be delivered during the vulnerable phase of the cardiac cycle, described as the 15 to 30 milliseconds before and after the T wave.

KEY FACTS

- ✓ Carcinoid heart disease—liver or lung metastases from carcinoid tumors produce the classic syndrome due to production of serotoninlike substances (toxic to cardiac valves)
- ✓ Carcinoid syndrome—cutaneous flushing, wheezing, and diarrhea
- ✓ Systemic lupus erythematosus—may involve any cardiac structure; features of involvement include Libman-Sacks endocarditis (which is more common in patients with antiphospholipid antibody syndrome)
- ✓ Scleroderma—cardiac involvement manifested by intramural coronary involvement and immune-mediated endothelial injury
- ✓ Rheumatoid arthritis—nearly all cardiac components may be affected; rheumatoid nodules in the conduction system can lead to heart block
- ✓ Marfan syndrome—cardiac involvement is common (mitral valve prolapse, aortic regurgitation due to aortic dilatation, or increased risk of aortic dissection)

The Heart and Pregnancy

Physiologic Changes of Pregnancy

Hormonal changes that begin at conception and continue throughout gestation result in an increase in plasma volume and red cell mass. However, the increase in plasma volume is larger than the increase in red cell mass; therefore, a relative anemia occurs. In addition to an increase in total intravascular volume, systemic vascular resistance decreases and heart rate slightly increases. The increase in preload and decrease in afterload allow for an increase in cardiac output by 30% to 50%, to supply the increased metabolic needs required to sustain the pregnancy. Overall blood pressure does not change substantially in association with the physiologic changes. Related to these physiologic changes, the physical examination during a normal pregnancy may have certain features to suggest cardiac compromise, including lower extremity edema, mildly increased jugular venous pressure, a soft short systolic murmur in the pulmonary area, an S_3, and a brisk and full carotid pulse.

Pregnancy and Cardiac Disease

Physical examination characteristics that should be considered abnormal in pregnancy include a diastolic murmur, a loud (3/6 or greater) systolic murmur, and an S_4. The physiologic changes that occur during pregnancy may unmask previously unrecognized maternal cardiac disease or may result in decompensation of previously known cardiac anomalies.

In general, cardiac lesions that do not allow for increased cardiac output (ie, valvular stenosis and ventricular dysfunction) are not well tolerated. Several situations provide a high risk to the mother such that pregnancy should be discouraged. These include pulmonary hypertension (pulmonary artery pressure >75% systemic systolic blood pressure), maternal aortopathy such as Marfan syndrome with an aortic dimension more than 40 mm, New York Heart Association class IV heart failure, and symptomatic severe aortic valve stenosis. The risk of a cardiac complication (ie, pulmonary edema, sustained arrhythmia requiring treatment, stroke, cardiac arrest, or cardiac death) during pregnancy in mothers without the above contraindications can be estimated using the Cardiac Disease in Pregnancy risk model (Circulation. 2001 Jul 31;104[5]:515-21) with refinements validated in a population of women with congenital heart disease (Circulation. 2006 Jan 31;113[4]:517-24). The risk factors to consider in this modified model include 1) New York Heart Association class III or IV or cyanosis, 2) previous cardiac event (arrhythmia, stroke, or heart failure), 3) left heart obstruction (eg, mitral valve area <2 cm^2, aortic valve area <1.5 cm^2, left ventricular outflow tract obstruction gradient >30 mm Hg), 4) systemic ventricular dysfunction (ejection fraction <40%), and 5) subpulmonary ventricular dysfunction or severe pulmonary valve regurgitation. Each risk factor present is given equal weight. The estimated risk of a cardiac event during pregnancy is 5% with 0 risk factors, 27% with 1 risk factor, and 75% with more than 1 risk factor; the most likely cardiac complication is pulmonary edema or arrhythmia.

Women who have cardiac complications during pregnancy need specialized care that may include initiation or titration of medication, bed rest, cardioversion, catheter-based intervention, cardiac surgery, and early delivery. Cardioversion can be performed with low risk to the fetus. If catheter-based intervention such as balloon valvuloplasty is performed, the fetus should be shielded from the ionizing radiation. Cardiac surgical procedures can be performed with good maternal and fetal outcomes, but fetal outcomes are best when the surgical intervention is performed during the second trimester.

Medical Therapy During Pregnancy

Many cardiac drugs cross the placenta but can be used safely when necessary. These include digoxin, quinidine, procainamide, β-adrenergic blockers, and verapamil. β-Adrenergic blockers are associated with fetal growth retardation, neonatal bradycardia, and hypoglycemia and should be used cautiously, but they are not contraindicated. Patients with hypertrophic cardiomyopathy may require high doses of β-adrenergic blockers, and thus fetal growth must be monitored for these patients.

Angiotensin-converting enzyme inhibitors (which may cause fetal renal dysgenesis), phenytoin (which may cause hydantoin syndrome and teratogenicity), and statins should be avoided in pregnancy. Warfarin is associated with fetal malformations and fetal loss and should be avoided during the first trimester, but it can be used in the second and third trimesters if there is a compelling need. If warfarin is used during pregnancy, alternative anticoagulation should be used during the last 4 weeks of gestation to prevent the fetus from having anticoagulation at the time of delivery. If warfarin is used at the time of labor, a cesarean-section delivery is indicated with general (not regional) anesthesia.

Delivery in the Clinical Setting of Cardiac Disease

Rapid hemodynamic swings occur during delivery. About 500 mL of blood is released into the circulation with each uterine contraction. Cardiac output increases with advancing labor, and oxygen consumption increases threefold. High-risk patients need careful monitoring, maternal and fetal ECG monitoring, careful analgesia and anesthesia to avoid hypotension, and limited Valsalva maneuver (“pushing”). Facilitated delivery may be needed.

Vaginal delivery is safer than cesarean section for most women with cardiac disease; the average blood loss is 500 mL with vaginal delivery and 800 mL with cesarean section. A cesarean section is typically performed only for obstetric indications, for urgent delivery for a woman in symptomatic heart failure, for delivery in a pregnancy complicated by progressive aortic enlargement, and for a woman who received anticoagulation with warfarin at the time of delivery. American Heart Association guidelines state that antibiotic prophylaxis is not needed in an uncomplicated vaginal delivery.

Box 4.1 • Hypertensive Disorders That Occur During Pregnancy

- Preeclampsia-eclampsia
  - Blood pressure increase after 20 weeks of gestation with proteinuria or any severe feature of preeclampsia, including the following:
    - Thrombocytopenia
    - Impaired liver function
    - New-onset renal insufficiency
    - Pulmonary edema
    - New-onset cerebral or visual disturbances
- Chronic hypertension (of any cause that predates pregnancy)
- Chronic hypertension with superimposed preeclampsia
- Gestational hypertension
  - Blood pressure increase after 20 weeks of gestation in the absence of proteinuria or any of the severe features of preeclampsia

Hypertension and Pregnancy

Four major hypertensive disorders occur in pregnant women (Box 4.1). Treatment of chronic or gestational hypertension during pregnancy with labetalol, nifedipine, or methyldopa is recommended. β-Adrenergic blockers are safe and efficacious but may cause fetal growth retardation and fetal bradycardia. The use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, and mineralocorticoid receptor antagonists is not recommended unless a compelling reason exists, such as the presence of proteinuric renal disease. Diuretics are effective because the hypertension of pregnancy is “salt-sensitive.” The Working Group on Hypertension in Pregnancy allows continuation of the use of diuretics if they had been prescribed before gestation.

Peripartum Cardiomyopathy

Peripartum cardiomyopathy (also known as *pregnancy-associated cardiomyopathy*) is a relatively rare form of systolic heart failure that occurs during the later months of pregnancy or the first 6 months after delivery. Multiple causes have been proposed, but none are validated. Patients generally present with dyspnea, edema, and reduced exercise tolerance. Because these symptoms mimic those of normal pregnancy and the early postpartum period, a high degree of suspicion is needed to make the diagnosis. Echocardiography generally shows left ventricular dilatation and reduced left ventricular ejection fraction. The clinical course ranges from rapid, complete recovery to end-stage heart failure requiring heart transplant to even death. Standard treatment of heart failure is used, with adjustments for women who are pregnant or lactating. Disease-specific therapeutic strategies, including prolactin blockade, are currently under investigation. Subsequent pregnancy may result in heart failure relapse, particularly for patients with persistent systolic dysfunction.

Key Definition

Peripartum cardiomyopathy: *rare form of systolic heart failure that occurs during later months of pregnancy or the first 6 months after delivery (also known as* pregnancy-associated cardiomyopathy*).*

KEY FACTS

- ✓ Abnormal physical examination findings—in pregnancy, these include a diastolic murmur, a loud systolic murmur, and an S_4
- ✓ High blood pressure during pregnancy—treat with labetalol, nifedipine, or methyldopa
- ✓ Drugs to avoid in pregnancy—angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, and mineralocorticoid receptor antagonists
- ✓ Peripartum cardiomyopathy—relatively rare form of systolic heart failure; occurs during later months of pregnancy or first 6 months after delivery

5

Cardiovascular Physical Examination

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Jugular Venous Pressure

J**ugular venous pressure** reflects right atrial pressure and the relationship between right atrial filling and emptying into the right ventricle (Figure 5.1). Changes in wave amplitude may indicate structural disease and rhythm changes. Normal jugular venous pressure is 6 to 8 cm H_2O. It is best evaluated with the patient supine at an angle of at least 45°. The right atrium lies 5 cm below the sternal angle, and thus the estimated jugular venous pressure equals the height of the jugular venous pressure above the sternal angle + 5 cm (Figure 5.1). The normal venous profile contains 3 positive waves and 2 negative waves. *Positive* waves are *a*, atrial contraction; *c*, closure of tricuspid valve; and *v*, atrial filling. *Negative* waves are the *x* descent (the downward motion of the right ventricle) and the *y* descent (the early right ventricular filling phase). The *a* wave comes just before the first heart sound, and the *v* wave comes during the ejection phase of the left ventricle.

The examiner must distinguish jugular venous pressure from carotid pulsations. Jugular venous pressure varies with respiration, is nonpalpable, and can be eliminated by applying gentle pressure at descent (diastole). When the pressure is increased, the clinician should consider biventricular failure, constrictive pericarditis, pericardial tamponade, cor pulmonale (especially pulmonary embolus), and superior vena cava syndrome.

Abnormalities of the venous waves suggest various cardiac conditions. Increased jugular venous pressure indicates possible fluid overload (common in congestive heart failure). The likelihood of congestive heart failure is increased 4 times if jugular venous pressure is increased. Increased jugular venous pressure can be associated with pulmonary embolus, superior vena cava syndrome, tamponade, and constrictive pericarditis. The inspection of individual wave profile may lend to the differential diagnosis. Large *a* waves may indicate tricuspid stenosis, right ventricular hypertrophy, or pulmonary hypertension (ie, increased right ventricular end-diastolic pressure). Pronounced or “cannon” *a* waves are due to atria contracting intermittently against a closed atrioventricular valve, a finding consistent with atrioventricular dissociation. Observation of a rapid *y* descent indicates constrictive pericarditis. Kussmaul sign, the paradoxic increase in jugular venous pressure with inspiration, occurs in pericardial tamponade, constrictive pericarditis, and right ventricular failure. Large, fused *cv* waves are due to tricuspid regurgitation.

Arterial Pulses

Palpation of the radial pulse is useful for heart rate. The brachial or carotid pulse is checked for contour and timing. It is important to assess the upstroke and pulse volume. **Tardus** is the timing and rate of rise of upstroke, and **parvus** is the pulse volume. Assessment should be conducted for radial- or brachial-femoral delay in patients with hypertension by checking radial, or brachial, and femoral pulses simultaneously. A delay is consistent with aortic coarctation.

Abnormalities of the arterial pulse and their associated conditions are listed in Table 5.1.

Key Definitions

Tardus: *timing and rate of rise of upstroke of arterial pulses.*

Parvus: *pulse volume of arterial pulses.*

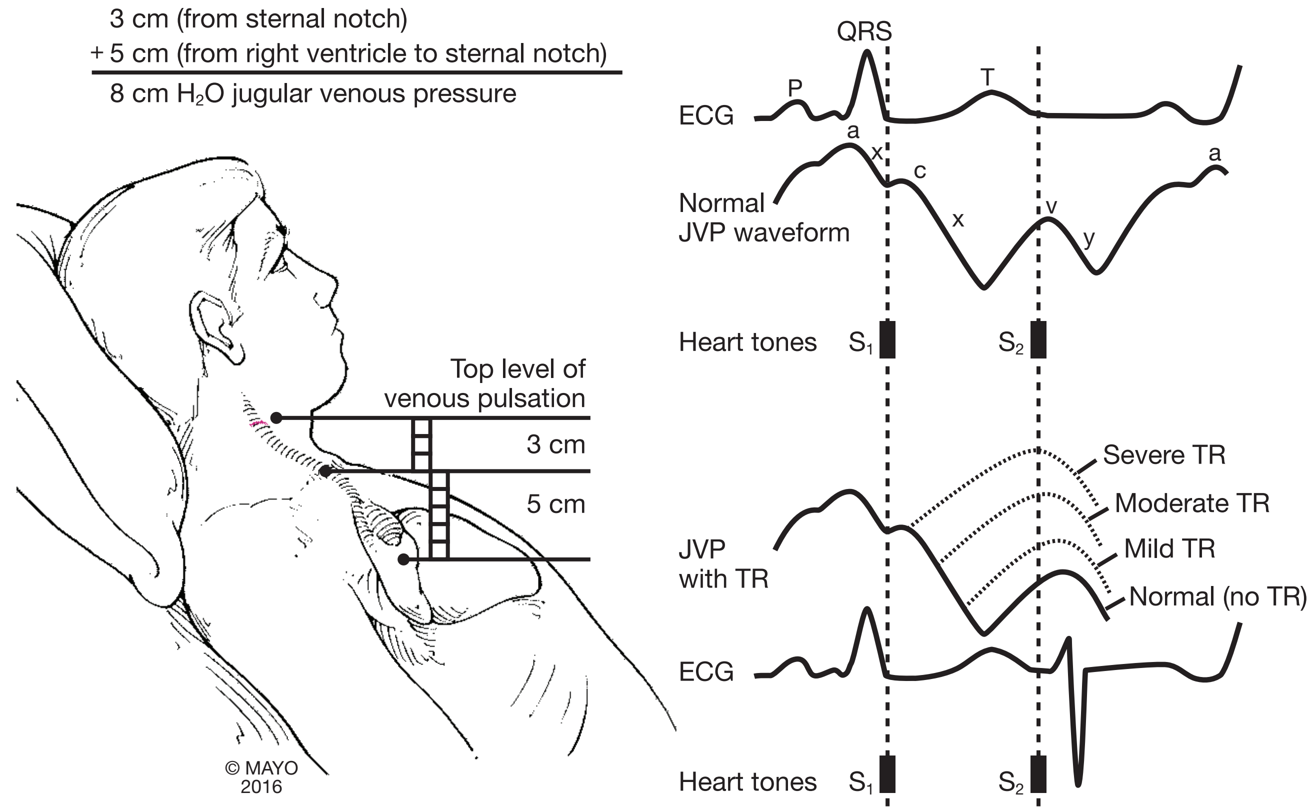
3 cm (from sternal notch)
+ 5 cm (from right ventricle to sternal notch)
8 cm H2O jugular venous pressure
Top level of venous pulsation
3 cm
5 cm
© MAYO 2016
QRS
ECG
P
T
a
x
c
x
v
y
a
Normal JVP waveform
Heart tones
S1
S2
Severe TR
Moderate TR
Mild TR
Normal (no TR)
JVP with TR
ECG
Heart tones
S1
S2

Figure 5.1. *Evaluation of Jugular Venous Pressure (JVP). ECG indicates electrocardiogram; S_1, first heart sound; S_2, second heart sound; TR, tricuspid regurgitation.*

Table 5.1 • Abnormalities of the Arterial Pulse and Their Associated Conditions

Abnormality	Associated Condition
Parvus (low volume) and tardus (delayed and slowed upstroke)	Aortic stenosis
Parvus only	Low-output cardiomyopathy
Bounding upstroke	Aortic regurgitation or arterioventricular fistulas and shunts
Bifid (2 systolic peaks)	Hypertrophic obstructive cardiomyopathy (from midsystolic obstruction)
Bisferiens (2 systolic peaks and a distinct systolic dip; occurs when a large volume is ejected rapidly into aorta)	Aortic regurgitation
Dicrotic (a systolic peak followed by diastolic pulse wave)	Left ventricular failure with hypotension, low output, and increased peripheral resistance
Pulsus paradoxus (exaggerated inspiratory decrease [>10 mm Hg] in pulse pressure)	Tamponade
Pulsus alternans (alternating strong and weak pulse)	Severely reduced left ventricular function

Apical Impulse

This is normally a discrete area of localized contraction, usually maximal at the fifth intercostal space in the midclavicular line and the size of a quarter (25-cent piece). Abnormalities of the apical impulse and their associated conditions are listed in Table 5.2.

Table 5.2 • Abnormalities of the Apical Impulse and Their Associated Conditions

Abnormality	Associated Condition
Displaced (laterally, downward, or both) with a weak, diffuse impulse	Cardiomyopathy
Sustained (may not be displaced)	Left ventricular hypertrophy Aortic stenosis (often with large *a* wave)
Trifid (or multifid)	Hypertrophic cardiomyopathy
Hyperdynamic, descended, and enlarged with rapid filling wave	Mitral regurgitation Aortic regurgitation
Tapping quality, localized, nondisplaced	Normal but may indicate mitral stenosis

Additional Cardiac Palpation

A palpable aortic valve component (A_2) at the right upper sternum suggests a dilated aorta (eg, aneurysm, dissection, severe aortic regurgitation, poststenotic dilatation in aortic stenosis, hypertension). Severe tricuspid regurgitation may cause a pulsatile liver palpable in the right epigastrium. Hepatojugular reflux (distention of the external jugular vein 3 or 4 beats after compression of the liver) may also occur in congestion of the liver with substantial fluid overload or tricuspid regurgitation. The apical impulse rotates medially and may be appreciated in the epigastrium (which can be confused with a pulsatile liver) in patients with severe emphysema. Right ventricular hypertrophy results in sustained lift, best appreciated in the fourth intercostal space along the left parasternal border. Diastolic overload (eg, atrial septal defect, anomalous pulmonary venous return) results in a vigorous outward and upward motion but may not be sustained. The pulmonary valve component (P_2) may be palpable in the second right intercostal space in marked pulmonary hypertension. This may be physiologic in slender people with a small anteroposterior diameter.

Thrills

Thrills indicate marked turbulent flow (eg, aortic stenosis, severe mitral regurgitation, ventricular septal defect) and distinction of a grade 4 murmur.

Heart Sounds

Knowledge of how the heart sounds are related to the cardiac cycle allows an understanding of cardiac auscultation (Figure 5.2). The cardiac cycle starts with atrial contraction; this increases ventricular pressure just before closure of the atrioventricular valves, which generates the first heart sound (S_1). There is a period of time while the left ventricle generates pressure, known as the *isovolumic contraction time*, when the atrioventricular and semilunar valves are closed. Normally silent semilunar valve openings then occur, followed by blood ejection from the left ventricle to the aorta, which creates the pulse. As the ventricle relaxes, aortic pressure decreases; this decrease closes the semilunar valves, creating the second heart sound (S_2). Another period follows when both sets of valves are closed. Pressure decreases to less than the left atrial pressure, leading to the usually silent opening of the atrioventricular valves. Early rapid filling followed by slow filling of the ventricles is followed by atrial contraction. The mnemonic for valve sequence—S_1-S_2 (right ventricular–left ventricular sequence)—is "**Many Things Are Possible**" (MTAP): S_1 = *m*itral opens before *t*ricuspid, and S_2 = *a*ortic closes before *p*ulmonary, under normal conditions.

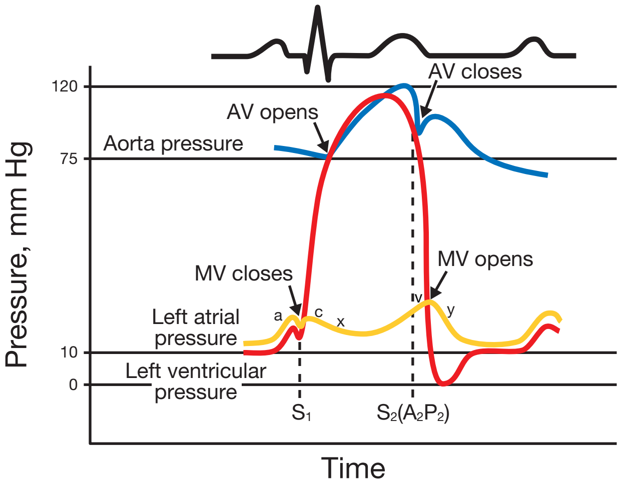

Figure 5.2. *The Normal Cardiac Cycle. A_2 indicates the aortic valve component of S_2; AV, aortic valve; MV, mitral valve; P_2, pulmonary valve component of S_2; S_1, first heart sound; S_2, second heart sound.*

KEY FACT

✓ Jugular venous pressure—reflects right atrial pressure and relationship between right atrial filling and emptying into the right ventricle; changes in amplitude may indicate structural disease and rhythm changes

Key Definition

***"Many Things Are Possible"**: MTAP mnemonic for valve sequence (S_1 = mitral opens before tricuspid, S_2 = aortic closes before pulmonary).*

First Heart Sound

S_1 consists of audible mitral valve closure followed by tricuspid valve closure. A loud S_1 occurs with mitral stenosis and short PR intervals (the mitral valve is open when the left ventricle begins to contract and then slaps shut). S_1 also is augmented in hypercontractile states (eg, fever, exercise, thyrotoxicosis, pheochromocytomas, anxiety, anemia). Conversely, S_1 is decreased if the mitral valve is heavily calcified and immobile (severe mitral stenosis) and with a long PR interval, poor left ventricular function, and rapid diastolic filling (due to premature mitral valve closure) as in aortic regurgitation.

Second Heart Sound

S_2 consists of aortic valve closure (A_2) followed by pulmonary valve closure (P_2). Intensity is increased by hypertension (ie, loud or tympanic A_2 with systemic hypertension and loud P_2 with pulmonary hypertension, with P_2 audible at apex). Intensity is decreased with heavily calcified valves (severe aortic

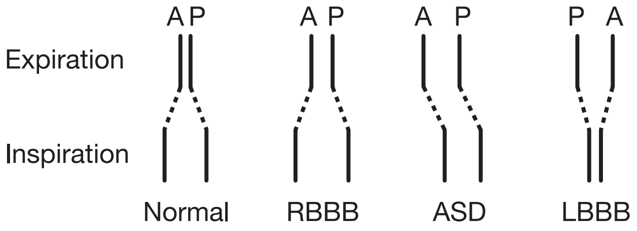

Figure 5.3. *Effects of Respiration and Conduction on the Second Heart Sound. The A indicates aortic closure; ASD, atrial septal defect; LBBB, left bundle branch block; P, pulmonary closure; RBBB, right bundle branch block.*

stenosis). Normally, the split between A_2 and P_2 widens on inspiration and narrows on expiration because of relatively increased blood return to the right heart during inspiration and greater capacitance of the lungs (Figure 5.3). This is reversed during expiration and is normal physiologic splitting of S_2. This is best heard in the left second intercostal space with the patient seated.

The interplay of multiple factors—electrical activation, duration of ventricular ejection, gradient across semilunar valves, and elastic recoil properties of the great vessels—can affect the timing of the closure of semilunar valves. Common types of splitting of the S_2 and their indicated conditions are listed in Table 5.3.

Third Heart Sound

The third heart sound (S_3) occurs in early diastole, coinciding with maximal early diastolic left ventricular filling. It is low pitched and best heard with the stethoscope bell. S_3 is associated with left ventricular volume overload (eg, aortic regurgitation, mitral regurgitation, cardiomyopathy). It is a normal variant in very fit young adults.

Table 5.3 • Common Types of Splitting of the Second Heart Sound and Their Indicated Conditions

Type	Indicated Condition
Physiologic	Normal splitting due to respiratory variation of blood flow On inspiration, P_2 moves farther from A_2, widening the split
Fixed	Atrial septal defect Widest split occurs with a combination of atrial septal defect and pulmonary stenosis
Paradoxic (delayed atrial closure; pulmonary valve closes first)	Left bundle branch block
Persistent	Right bundle branch block A_2 and P_2 are separated because of delayed electromechanical activation of right ventricle Inspiration accentuates the effect

Abbreviations: A_2, aortic valve closure; P_2, pulmonary valve closure.

Fourth Heart Sound

The fourth heart sound (S_4) is low pitched, best heard with the stethoscope bell, and loudest at the apex. This sound occurs with the atrial "kick" as blood is forced into the left ventricle by atrial contraction against a stiff and noncompliant left ventricle. An S_4 may be heard in aortic stenosis, systemic hypertension, hypertrophic cardiomyopathy, and ischemia. It cannot occur in atrial fibrillation because of the loss of atrial contraction.

KEY FACTS

- ✓ First heart sound—a loud S_1 occurs with mitral stenosis and short PR intervals (mitral valve is open when left ventricle begins to contract and then slaps shut)
- ✓ Second heart sound—intensity is increased by hypertension (loud or tympanic A_2 with systemic hypertension; loud P_2 with pulmonary hypertension, with P_2 audible at apex)
- ✓ Second heart sound—intensity is decreased with heavily calcified valves (severe aortic stenosis)
- ✓ Third heart sound—associated with left ventricular volume overload (eg, aortic regurgitation, mitral regurgitation, cardiomyopathy)
- ✓ Fourth heart sound—may be heard in aortic stenosis, systemic hypertension, hypertrophic cardiomyopathy, and ischemia
- ✓ Fourth heart sound—cannot occur in atrial fibrillation because of loss of atrial contraction

Opening Snap

Opening snap is an early diastolic sound caused by opening of the pathologic rheumatic mitral valve. It is virtually always caused by mitral stenosis. With severe mitral stenosis, the left atrial pressure is very high and thus the valve opens earlier, and the interval is less than 60 to 80 milliseconds.

Murmurs

The specific murmurs are discussed with the individual valvular lesions described in Chapter 10, "Valvular and Congenital Heart Diseases," but some broad guidelines are presented here.

A systolic ejection murmur begins after S_1 and ends before S_2. It may have a diamond-shaped sound quality with crescendo and

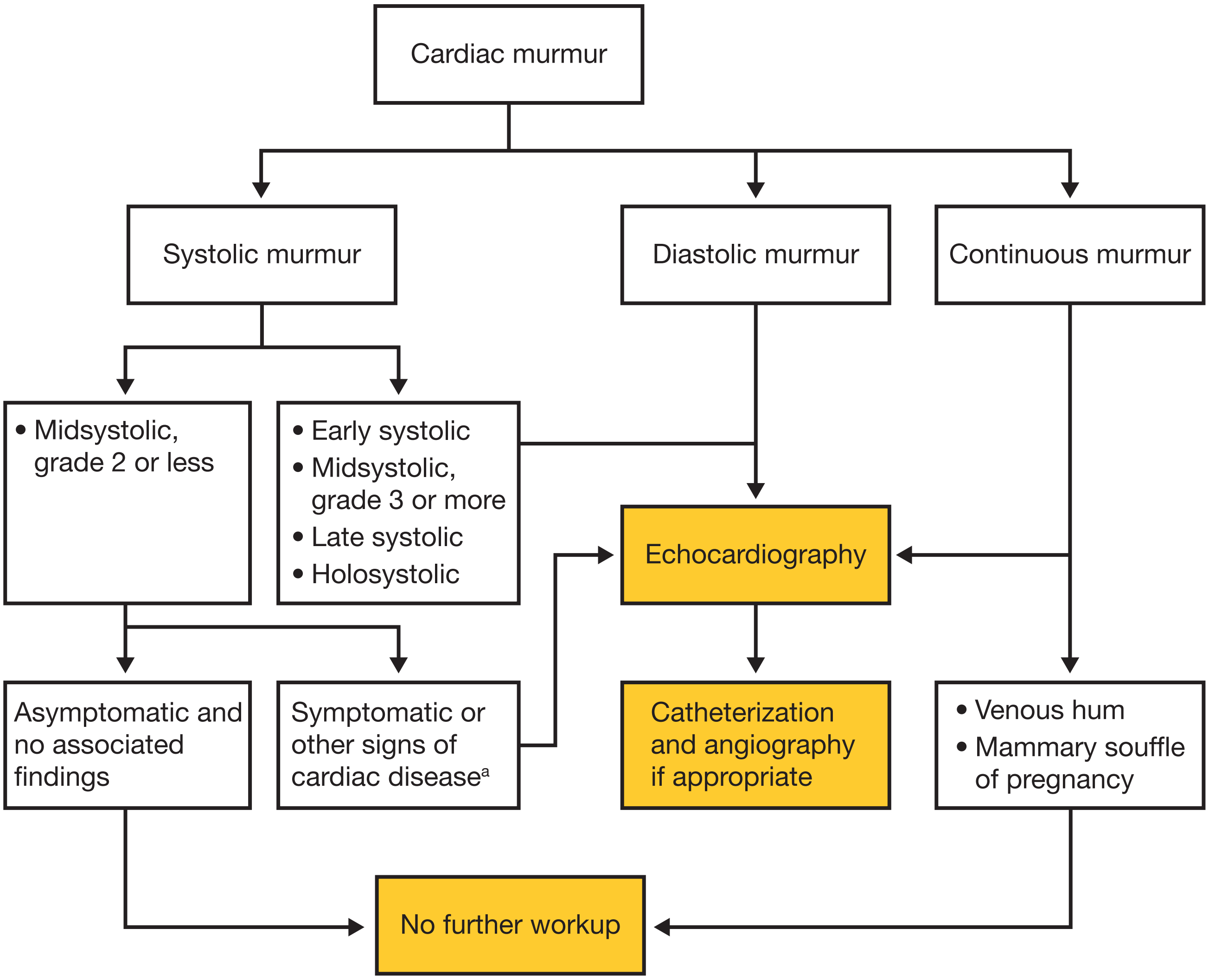
Cardiac murmur
Systolic murmur
Diastolic murmur
Continuous murmur
• Midsystolic, grade 2 or less
• Early systolic
• Midsystolic, grade 3 or more
• Late systolic
• Holosystolic
Echocardiography
Asymptomatic and no associated findings
Symptomatic or other signs of cardiac disease[a]
Catheterization and angiography if appropriate
• Venous hum
• Mammary souffle of pregnancy
No further workup

Figure 5.4. *Recommendations for Evaluating Heart Murmurs.*

[a] If electrocardiography or chest radiography has been performed and the results are abnormal, echocardiography is recommended.

(Further details about systolic murmurs are published at https://doi.org/10.1161/CIRCULATIONAHA.108.190748. From Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, et al; 2006 Writing Committee Members; American College of Cardiology/American Heart Association Task Force. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease]: endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2008 Oct 7;118[15]:e523-661. Epub 2008 Sep 26; used with permission.)

decrescendo components. In general, a more severe obstruction (a narrower valve orifice) causes a louder, later-peaking murmur. An *ejection click* may precede a bicuspid (aortic or pulmonary) valve murmur if the valve pliability is preserved. A holosystolic murmur engulfs S_1 and S_2 and occurs when blood moves from a very high-pressure system to a low-pressure system, such as in mitral regurgitation and ventricular septal defect. Diastolic murmurs are always abnormal. Echocardiography should be considered in this clinical setting if a systolic murmur of grade 3 or higher is heard or if there are other signs or symptoms of cardiac disease (Figure 5.4).

Certain maneuvers alter cardiac murmurs. *Inspiration* increases venous return, increasing right-sided sounds (S_3 and S_4) and murmurs (tricuspid and pulmonary stenosis, and tricuspid and pulmonary regurgitation). The *Valsalva maneuver* increases intrathoracic pressure, inhibiting venous return and thus decreasing preload. Most cardiac murmurs and sounds diminish in intensity during the Valsalva maneuver because of decreased ventricular filling and cardiac output. The exception is hypertrophic obstructive cardiomyopathy, in which the murmur increases because of dynamic left ventricular outflow obstruction accentuated by decreased preload. The Valsalva

Table 5.4 • Effects of Physical Maneuvers and Other Factors on Valvular Diseases

Maneuver or Factor	Result	Mitral Regurgitation	MVP	Aortic Stenosis	HOCM
Amyl nitrite	↓ afterload	↓	↑/0	↑	↑
Valsalva	↓ preload	↓	↑	↓	↑
Handgrip	↑ afterload	↑	↓/0	↓	↓
Post-PVC	↑ contractility ↓ afterload	=	↓	↑	↑[a]

Abbreviations: HOCM, hypertrophic obstructive cardiomyopathy; MVP, mitral valve prolapse; PVC, premature ventricular complex.

[a] Although the murmur increases, the peripheral pulse decreases because of the increase in outflow obstruction.

maneuver is the classic way to distinguish between the murmurs of aortic stenosis and hypertrophic cardiomyopathy. *Handgrip* increases cardiac output and systemic arterial pressure, decreasing the gradient across a stenotic aortic valve. A *change in posture* from supine to upright causes decreased venous return, reducing stroke volume and thus causing a reflex increase in heart rate and peripheral resistance. *Squatting* and the Valsalva maneuver have opposite hemodynamic effects. Squatting increases peripheral resistance and venous return. *Amyl nitrite* pharmacologically decreases afterload. The amyl nitrite is inhaled and transiently lowers blood pressure, increasing the murmurs of hypertrophic cardiomyopathy and aortic stenosis. Its main use is to determine the gradient in patients with dynamic left ventricular outflow obstruction due to hypertrophic cardiomyopathy. The effects of maneuvers are shown in Table 5.4.

6 Heart Failure and Cardiomyopathies

FARRIS K. TIMIMI, MD

Heart Failure

Heart failure is a clinical syndrome characterized by inability of the heart to maintain adequate cardiac output to meet the metabolic demands of the body while still maintaining normal or near-normal ventricular filling pressures. Heart failure may be present at rest, but often it is symptomatic only during exertion because of the dynamic nature of cardiac demands. For optimal treatment of heart failure, the mechanism, the underlying cause, and any reversible precipitating factors must be identified. Typical manifestations of heart failure are dyspnea and fatigue, limiting activity tolerance, and fluid retention leading to pulmonary or peripheral edema. These abnormalities do not always occur simultaneously. Dyspnea may be due to impaired cardiac output, increased filling pressures, or both.

Key Definition

Heart failure: *a clinical syndrome characterized by inability of the heart to maintain adequate cardiac output to meet the metabolic demands of the body while still maintaining normal or near-normal ventricular filling pressures.*

The symptomatic expression of cardiac disease, heart failure, usually arises sometime after cardiac disease is established. The American College of Cardiology and the American Heart Association stages of heart failure (Figure 6.1) emphasize that symptoms follow an asymptomatic phase of cardiac dysfunction, which highlights the opportunity to preclude the development of heart failure by early intervention. In symptomatic patients, it can often be challenging to determine whether symptoms are cardiac due to structural disease or whether they are coincidental noncardiac symptoms coexisting with asymptomatic structural disease.

Heart failure may result from abnormalities of the pericardium, myocardium, endocardium, cardiac valves, or vascular or renal systems (eg, hyperreninemic pulmonary edema). Most commonly, it is due to impaired left ventricular (LV) myocardial function. In approximately 50% of cases, the left ventricle is enlarged and there is abnormal contractile function with reduced ejection fraction (<50%). This type is referred to as *dilated cardiomyopathy*. The ejection fraction is normal in the other 50%. This second type is referred to as *heart failure with preserved ejection fraction*. Isolated right ventricular failure can occur; however, the majority of cases of heart failure involve either the left ventricle alone or the left ventricle with associated right ventricular dysfunction. High ventricular filling pressures can cause dyspnea and edema.

Presentation

Patients may present with asymptomatic ventricular dysfunction (usually, dilated ventricles with reduced ejection fraction). These patients do not have heart failure, and they can usually be treated as outpatients; their treatment is discussed later in this chapter. Patients with heart failure (ie, symptoms and signs) may present either as outpatients or to acute care facilities, often depending on symptom severity. This heterogeneous group is said to have acute decompensated heart failure and includes patients presenting for the first time with heart failure and patients presenting with a decompensation of known heart failure.

Hospitalization is advisable when hypotension, worsening renal function, altered mentation, dyspnea at rest, significant arrhythmias (eg, new atrial fibrillation), or other complications such as disturbed electrolyte levels are present or outpatient care options are lacking (Box 6.1). Patients without these factors who have exertional symptoms exclusively, are not severely congested

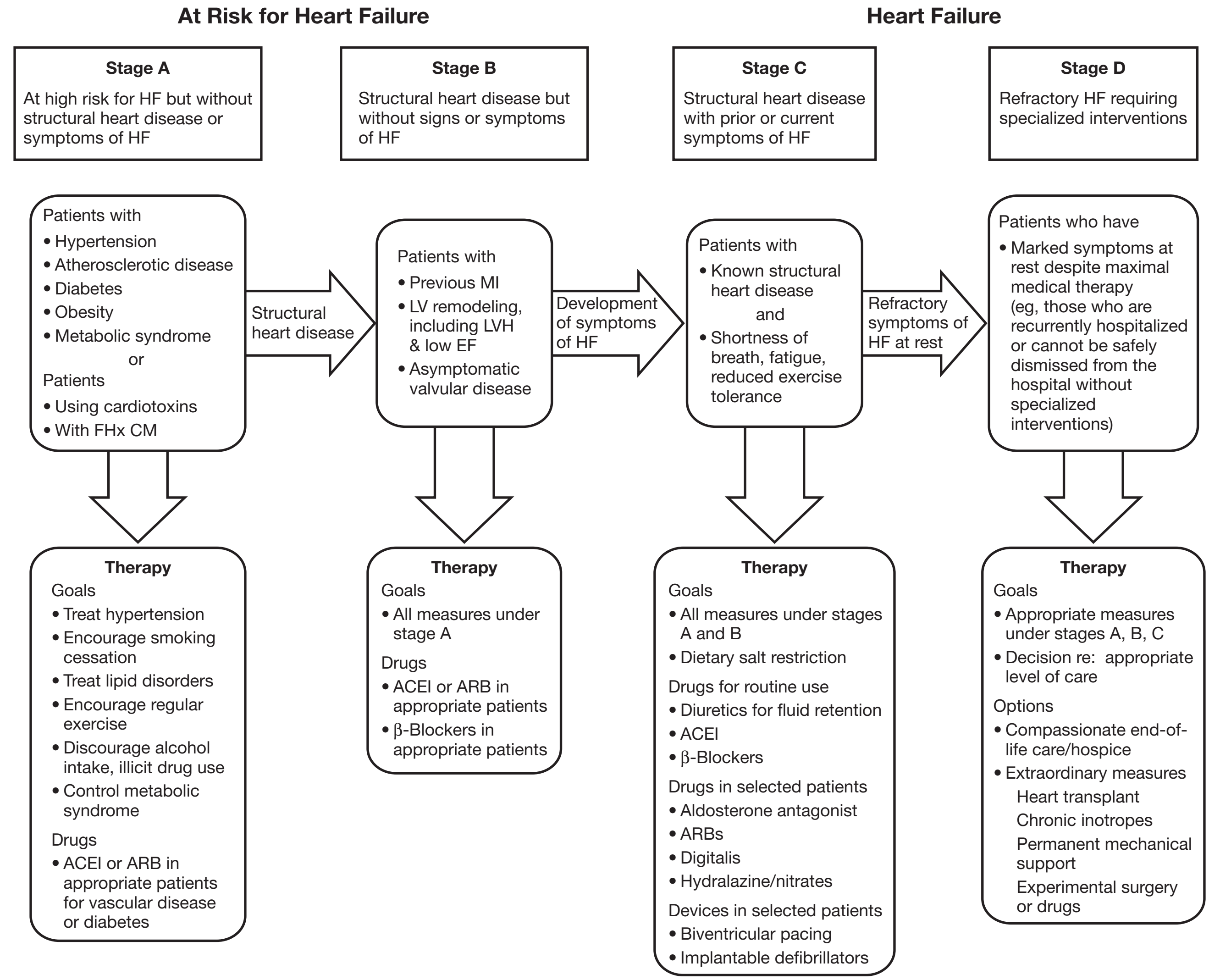
At Risk for Heart Failure
Heart Failure
Stage A
At high risk for HF but without structural heart disease or symptoms of HF
Stage B
Structural heart disease but without signs or symptoms of HF
Stage C
Structural heart disease with prior or current symptoms of HF
Stage D
Refractory HF requiring specialized interventions
Patients with
• Hypertension
• Atherosclerotic disease
• Diabetes
• Obesity
• Metabolic syndrome
or
Patients
• Using cardiotoxins
• With FHx CM
Structural heart disease
Patients with
• Previous MI
• LV remodeling, including LVH & low EF
• Asymptomatic valvular disease
Development of symptoms of HF
Patients with
• Known structural heart disease
and
• Shortness of breath, fatigue, reduced exercise tolerance
Refractory symptoms of HF at rest
Patients who have
• Marked symptoms at rest despite maximal medical therapy (eg, those who are recurrently hospitalized or cannot be safely dismissed from the hospital without specialized interventions)
Therapy
Goals
• Treat hypertension
• Encourage smoking cessation
• Treat lipid disorders
• Encourage regular exercise
• Discourage alcohol intake, illicit drug use
• Control metabolic syndrome
Drugs
• ACEI or ARB in appropriate patients for vascular disease or diabetes
Therapy
Goals
• All measures under stage A
Drugs
• ACEI or ARB in appropriate patients
• β-Blockers in appropriate patients
Therapy
Goals
• All measures under stages A and B
• Dietary salt restriction
Drugs for routine use
• Diuretics for fluid retention
• ACEI
• β-Blockers
Drugs in selected patients
• Aldosterone antagonist
• ARBs
• Digitalis
• Hydralazine/nitrates
Devices in selected patients
• Biventricular pacing
• Implantable defibrillators
Therapy
Goals
• Appropriate measures under stages A, B, C
• Decision re: appropriate level of care
Options
• Compassionate end-of-life care/hospice
• Extraordinary measures
Heart transplant
Chronic inotropes
Permanent mechanical support
Experimental surgery or drugs

Figure 6.1. *Stages in the Development of HF and Recommended Therapy by Stage. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; EF, ejection fraction; FHx CM, family history of cardiomyopathy; HF, heart failure; LV, left ventricular; LVH, left ventricular hypertrophy; MI, myocardial infarction.*

(Adapted from Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al; American College of Cardiology Foundation; American Heart Association. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 2009 Apr 14;53[15]:e1–90. Erratum in: J Am Coll Cardiol. 2009 Dec 15;54[25]:2464 and Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation. 2009 Apr 14;119[14]:e391–479. Epub 2009 Mar 26. Erratum in: Circulation. 2010 Mar 30;121[12]:e258; used with permission.)

on examination, and have adequate vascular perfusion (warm extremities, adequate blood pressure) may receive treatment as outpatients. The stages of heart failure development and management are outlined in Figure 6.1.

Diagnosis

The clinical diagnosis of heart failure is based on symptoms, physical findings, and chest radiography. Symptoms typically include some combination of dyspnea, fatigue, and fluid retention. The dyspnea may occur with exertion or with recumbency. Physical findings include evidence of low cardiac output, volume overload, or both. Such evidence includes narrow pulse pressure, poor peripheral perfusion, jugular venous distention, hepatojugular reflux, peripheral edema, ascites, and dull lung bases suggestive of pleural effusions. Lung crackles usually represent atelectatic compression rather than fluid in the alveoli,

Box 6.1 • Conditions That Prompt Hospitalization in Heart Failure

- Hypotension
- Worsening renal function
- Altered mentation
- Dyspnea at rest
- Severe arrhythmias
- Disturbed electrolyte levels
- Lack of outpatient care

the latter being more common in *acute* heart failure. In contrast, exacerbation of *chronic* heart failure may be associated with less notable pulmonary findings as a product of chronic pulmonic lymphatic recruitment. Edema usually affects the lower extremities but can also affect the abdomen. Cardiac findings include abnormalities of the cardiac apex (enlarged, displaced, sustained point of maximal impulse) and gallop rhythms. The liver may be enlarged, pulsatile, and tender when right heart failure is present. Clinical signs indicating high- and low-output heart failure could aid in patient treatment (Table 6.1). The symptoms and signs of heart failure described above are nonspecific and can occur in other conditions. Heart failure diagnosis is probabilistic and best made through use of the modified Framingham criteria (Box 6.2).

Table 6.1 • Management of High-Output and Low-Output Heart Failure

	Congestion at Rest	
Perfusion at Rest	**No**	**Yes**
High	Warm and dry PCWP normal CI normal (compensated)	Warm and wet PCWP increased CI normal ↓ Hospitalize ± Nesiritide or vasodilators[a] Diuretics
Low	Cold and dry PCWP low or normal CI decreased ↓ Hospitalize Cautious hydration Inotropic drug[b]	Cold and wet PCWP increased CI decreased ↓ Hospitalize Nesiritide or vasodilator[a] Diuretics

Abbreviations: CI, cardiac index; ↓, decreased; PCWP, pulmonary capillary wedge pressure; ±, patient may or may not require hospitalization, depending on clinical assessment.

[a] Vasodilator: nitroglycerin or nitroprusside.

[b] Inotropic drug: milrinone or dobutamine.

Box 6.2 • Modified Framingham Criteria for Clinical Diagnosis of Congestive Heart Failure[a]

Major Criteria	**Minor Criteria**
PND	Peripheral edema
Orthopnea	Night cough
Increased JVP	DOE
Rales	Hepatomegaly
Third heart sound	Pleural effusion
Chest radiography	Heart rate >120 beats per minute
Cardiomegaly	Weight loss ≥4.5 kg in 5 days with diuretic
Pulmonary edema	

Abbreviations: DOE, dyspnea on exertion; JVP, jugular venous pressure; PND, paroxysmal nocturnal dyspnea.

[a] Congestive heart failure is validated if 2 major or 1 major and 2 minor criteria are present concurrently.

Data from Senni M, Tribouilloy C, Rodeheffer R, Jacobsen S, Evans J, Kent B, et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. Circulation. 1998 Nov 24;98(21):2282–9.

According to the modified Framingham criteria, the simultaneous presence of 2 major or of 1 major and 2 minor criteria satisfies the clinical diagnosis of congestive heart failure. Exertional dyspnea does not have the same weight as paroxysmal nocturnal dyspnea or orthopnea, and edema does not have the same diagnostic weight as increased venous pressure. Patients with low-output heart failure may not have findings of volume overload (congestion) and thus may not satisfy Framingham criteria.

Increased intracardiac pressure or chamber dilatation leads to increased production of natriuretic peptides, substances produced by the heart. Accordingly, measurement of B-type natriuretic peptide or N-terminal prohormone of brain natriuretic peptide complements the clinical diagnosis of heart failure. In general, the degree of increase in natriuretic peptides reflects the degree of myocardial dysfunction. However, increased levels of these peptides do not distinguish systolic from diastolic, left from right, or acute from chronic cardiac dysfunction. Interpreting these levels has caveats (Box 6.3). In addition, levels

Box 6.3 • Pitfalls in the Interpretation of NP Value

NP Greater Than Expected	**NP Less Than Expected**
Female sex	Obesity
Elderly age	Acute heart failure
Renal failure	Heart failure due to mitral stenosis
	Constriction

Abbreviation: NP, natriuretic peptide.

vary substantially—up to 50%—in patients who are hemodynamically stable.

The utility of the natriuretic peptide values for diagnosis of heart failure has been best shown in patients without prior known cardiac disease. Interpretation of intermediately increased levels can be difficult in patients with a prior history of ventricular dysfunction or heart failure who are receiving medical treatment. The negative predictive value of normal natriuretic peptide levels (in the absence of constriction, morbid obesity, or mitral stenosis) is more powerful than their positive predictive value. Natriuretic peptide values are most useful in patients without a prior diagnosis of heart failure and in patients not receiving treatment of heart failure.

Management of Acute Heart Failure

At the time of initial diagnosis, the common alternative diagnoses of pulmonary embolism and exacerbation of chronic obstructive pulmonary disease must be excluded. Clinical stratification guides initial treatment (usually parenteral) (Figure 6.2).

When clinical improvement begins, treatment is adjusted to optimize hemodynamics, minimize symptoms, and allow transition to oral medications. The mechanism of heart failure and precipitating factors are defined, patient and family education is provided, and dismissal (including timely follow-up) is planned.

Mechanisms

Selection of proper therapy depends on correctly identifying the mechanism of heart failure. A simple categorical framework is given in Table 6.2. LV myocardial dysfunction is the most common cause of heart failure. Accurate diagnosis is essential because treatment and prognosis are based on the cause of heart failure. Diagnosis is initially based on physical examination and noninvasive testing, such as echocardiography or radionuclide angiography.

Precipitating Factors

New-onset or worsening symptoms of heart failure may represent only natural disease progression. However, 1 or more precipitating factors may be responsible for symptomatic deterioration (Box 6.4). If these factors are not identified and corrected, symptoms of heart failure often return after initial therapy. The most common precipitants are dietary indiscretion (eg, sodium, excess fluid, alcohol), medication nonadherence (due to cost, regimen complexity, or lack of patient understanding), and suboptimally controlled hypertension.

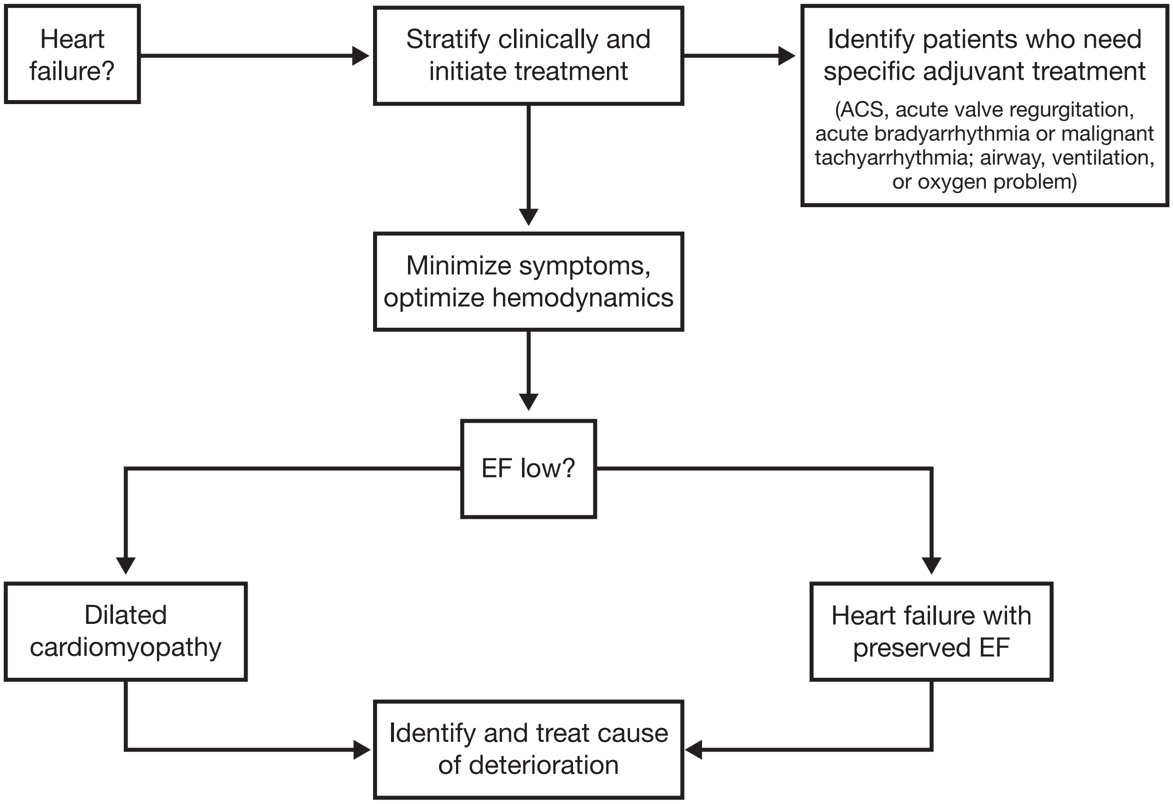
Heart failure?
Stratify clinically and initiate treatment
Identify patients who need specific adjuvant treatment
(ACS, acute valve regurgitation, acute bradyarrhythmia or malignant tachyarrhythmia; airway, ventilation, or oxygen problem)
Minimize symptoms, optimize hemodynamics
EF low?
Dilated cardiomyopathy
Heart failure with preserved EF
Identify and treat cause of deterioration

Figure 6.2. *Approach to Acute Heart Failure. ACS indicates acute coronary syndrome; EF, ejection fraction.*

Table 6.2 • Causes of Heart Failure and Its Treatment

Cause	Treatment
Myocardial	
Dilated cardiomyopathy (including ischemic)	Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-adrenergic blockers (eg, carvedilol, metoprolol succinate, bisoprolol), diuretics, aldosterone antagonists, nitrates, digoxin, nitrates and hydralazine in combination, transplant, coronary revascularization, left ventricular aneurysmectomy (surgical ventricular remodeling), cardiac resynchronization therapy, cardiac defibrillator
Hypertrophic cardiomyopathy	β-Adrenergic blockers, verapamil, disopyramide, surgical myectomy, septal alcohol ablation, dual-chamber pacing
Restrictive cardiomyopathy	Diuretics, heart transplant, treatment of underlying systemic disease
Pericardia	
Tamponade	Pericardiocentesis
Constrictive pericarditis	Pericardiectomy
Valvular	Valve repair or replacement
Hypertension	Antihypertensive treatment
Pulmonary hypertension	Prostacyclin infusion, calcium channel blockers, heart-lung transplant, endothelin antagonists, phosphodiesterase type 5 inhibitor
High output	
Hyperthyroidism, Paget disease, arteriovenous fistula	Correction of underlying cause

Box 6.4 • Precipitating Factors in Heart Failure

Diet (excessive intake of sodium, fluid, alcohol)
Noncompliance with medication or inadequate dosing
Sodium-retaining medications (NSAIDs)
Infection (bacterial or viral)
Myocardial ischemia or infarction
Arrhythmia (atrial fibrillation, bradycardia)
Breathing disorders of sleep
Worsening renal function
Anemia
Metabolic (hyperthyroidism, hypothyroidism)
Pulmonary embolus

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

Evaluation should consist of 1) a medical history, which includes sodium and fluid intake, medication use and compliance, and sleep history from bedroom partners; 2) chest radiography to look for pneumonitis or pleural effusions; 3) electrocardiography and measurement of cardiac biomarkers to document heart rhythm and identify myocardial ischemia or injury; and 4) cultures of blood, urine, and sputum as suggested by patient history. Other tests should include determination of complete blood cell count and levels of TSH (thyrotropin) and creatinine.

KEY FACTS

- ✓ In symptomatic heart failure—can often be challenging to determine whether symptoms are cardiac due to structural disease or coincidental noncardiac coexisting with asymptomatic structural disease
- ✓ In heart failure—hospitalization is advised when hypotension, worsening renal function, altered mentation, dyspnea at rest, clinically important arrhythmias, or other complications are present or patient care options are lacking
- ✓ Heart failure—a clinical diagnosis based on symptoms, physical findings, and chest radiography
- ✓ Symptoms of heart failure—some combination of dyspnea, fatigue, and fluid retention
- ✓ Modified Framingham criteria—used to make a probabilistic clinical diagnosis of heart failure
- ✓ B-type natriuretic peptide and N-terminal prohormone of brain natriuretic peptide—measurement of these peptides complements the clinical diagnosis of heart failure; their degree of increase reflects the degree of myocardial dysfunction
- ✓ Increased levels of B-type natriuretic peptide or N-terminal prohormone of brain natriuretic peptide—do not distinguish systolic from diastolic, left from right, or acute from chronic cardiac dysfunction
- ✓ Negative predictive value of normal natriuretic peptide levels—more powerful than their positive predictive value

Cardiomyopathies

Cardiomyopathies are divided into primary and secondary, and the primary disorders are further subdivided as genetic, acquired, or mixed. This classification scheme accounts for progressive understanding of this heterogeneous group of disorders. However, the previous phenotypic classification scheme of

Table 6.3 • Anatomical and Pathophysiologic Processes for Each Cardiomyopathy Type

Cardiomyopathy Type	Left Ventricular Cavity Size	Left Ventricular Wall Thickness	Ejection Fraction	Diastolic Function	Other
Dilated	↑	N/↑	↓	↓	
Hypertrophic	↓/N	↑	↑	↓	Left ventricular outflow obstruction
Restrictive	N/↑	N	N	↓	

Abbreviation and symbols: ↓, decreased; N, normal; ↑, increased.

dilated, hypertrophic, and restrictive diseases can be more useful for guiding clinical understanding and management. The different anatomical and pathophysiologic processes for each cardiomyopathy are listed in Table 6.3.

Dilated Cardiomyopathy

Pathology and Etiology

The major abnormality in dilated cardiomyopathy is a remodeled left ventricle, characterized by dilatation and reduced ejection fraction. LV end-diastolic pressure is typically increased. The increased filling pressures and low cardiac output cause dyspnea and fatigue. *Idiopathic* dilated cardiomyopathy indicates LV dysfunction without a known cause. The right ventricle may be normal, hypertrophied, or dilated.

In many patients with dilated cardiomyopathy, the cause is genetic, and up to 30% have at least 1 identifiable affected family member. Other causes of LV dysfunction include severe coronary artery disease—the most common cause in the United States—(hibernating myocardium), previous infarction, uncontrolled hypertension, ethanol abuse, myocarditis, hyperthyroidism or hypothyroidism, postpartum cardiomyopathy, toxins and drugs (including doxorubicin and trastuzumab), tachycardia-induced cardiomyopathy, infiltrative cardiomyopathy (eg, hemochromatosis, sarcoidosis), AIDS, and pheochromocytoma.

Clinical Presentation

The presentation of dilated cardiomyopathy is highly variable. A patient may be asymptomatic and the diagnosis prompted by examination, chest radiography, electrocardiography (ECG), or imaging findings. Patients may have symptoms of mild to severe heart failure (New York Heart Association [NYHA] functional class II-IV). Atrial and ventricular arrhythmias are common in dilated cardiomyopathy. Physical examination may indicate increased jugular venous pressure, a right ventricular lift (when there is right heart involvement), low-volume upstroke of the carotid artery, displaced and sustained LV impulse (possibly with a rapid filling wave), audible third or fourth heart sounds, and an apical systolic murmur of mitral regurgitation. Pulsus alternans may occur in patients with advanced heart failure. Pulmonary examination may have normal results or indicate crackles or evidence of pleural effusion.

The ECG is almost always abnormal and frequently indicates LV hypertrophy, intraventricular conduction delay, or bundle branch block. Rhythm abnormalities may include premature atrial contractions, atrial fibrillation, premature ventricular contractions, or short bursts of ventricular tachycardia. The chest radiograph often shows LV enlargement and pulmonary venous congestion. The diagnosis is based on clinical signs and symptoms coupled with findings of LV enlargement and reduced ejection fraction, which can be measured with echocardiography, radionuclide angiography, left ventriculography, cine computed tomography, or magnetic resonance imaging.

Evaluation

After diagnosis, treatable secondary causes of LV dysfunction should be sought. Tests of thyroid function should be done to exclude hyperthyroidism or hypothyroidism. Transferrin levels should be measured to screen for hemochromatosis. Measurement of the serum angiotensin-converting enzyme (ACE) level should be considered if sarcoidosis is a possibility. Metanephrine levels should be measured if there is a history of severe labile hypertension or unusual spells. Ethanol or drug abuse history should be obtained.

In severe coronary artery disease, reversible LV dysfunction can be caused by hibernating myocardium. With revascularization, LV function may improve gradually. Identification of patients with severe hibernating myocardium is difficult. Currently, the reference standard is positron emission tomography to evaluate metabolic activity. Viability protocols used in stress echocardiography and radionuclide perfusion imaging are more widely available than positron emission tomography and are useful for identifying hibernating myocardium.

Tachycardia-induced cardiomyopathy can occur in patients with prolonged periods of tachycardia (usually atrial fibrillation or flutter or prolonged atrial tachycardia). Because systolic dysfunction can be completely reversed with treatment of tachycardia, identification of these causes is important.

Acute myocarditis may cause LV dysfunction; the natural history is unknown. Many patients have development of persistent LV dysfunction, whereas others have improvement with time. Thus, it is necessary to remeasure LV function 3 to 6 months after diagnosis and treatment. Endomyocardial biopsy may help diagnose myocarditis. Immunosuppressive therapy does not improve outcome and should be reserved for patients with giant cell myocarditis, concomitant skeletal myositis, or clinical deterioration despite standard pharmacologic therapy.

Pathophysiology

The hemodynamic, pathophysiologic, and biologic aspects of heart failure must be appreciated to understand treatment of dilated cardiomyopathy. **Preload** is the ventricular volume at the end of diastole (end-diastolic volume). Typically, when it is increased, stroke volume increases. The relationship of stroke volume to preload is illustrated by the preload Starling curve (Figure 6.3). **Afterload** is the tension, force, or stress on the ventricular wall muscle fibers after fiber shortening begins. LV afterload is increased by aortic stenosis and systemic hypertension but is decreased by mitral regurgitation. Ventricular enlargement increases afterload.

Key Definitions

Preload: *the ventricular volume at the end of diastole (end-diastolic volume).*

Afterload: *the tension, force, or stress on the ventricular wall muscle fibers after fiber shortening begins.*

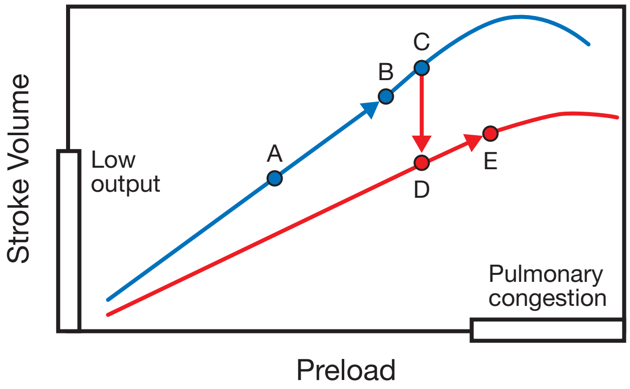

Figure 6.3. *Starling Mechanism Curve. Blue line is patient with normal contractility; red line is patient with depressed systolic function. Normally, stroke volume depends on preload of the heart. Increasing preload increases stroke volume (A to B). Myocardial dysfunction causes a shift of the curve downward and to the right (C to D), causing a severe decrease in stroke volume, which in turn leads to symptoms of fatigue and lethargy. The compensatory response to the decreased stroke volume is an increase in preload (D to E). Because the diastolic pressure-volume relationship is curvilinear, increased left ventricular volume produces increased left ventricular end-diastolic pressure, causing symptoms of pulmonary congestion. The flat portion of the curve at its upper end is noted; little increase occurs in stroke volume for increase in preload.*

Figure 6.4 illustrates the neurohormonal response to decreased myocardial contractility. Decreased cardiac output activates baroreceptors and the sympathetic nervous system. Stimulation of the sympathetic nervous system causes increased heart rate and contractility. α-Stimulation of the arterioles causes increases in afterload. The renin-angiotensin system is activated by sympathetic stimulation, decreased renal blood flow, and decreased renal sodium, in turn activating aldosterone release, causing increased renal retention of sodium, which leads to pulmonary congestion. Low renal blood flow causes renal sodium retention. Increased angiotensin II causes vasoconstriction and increased afterload. In congestive heart failure, the compensatory mechanisms that increase preload eventually cause a malcompensatory increase in afterload, in turn causing further decrease in stroke volume.

In the subacute and long-term stages of heart failure, neurohormonal (eg, adrenergic, angiotensin II) and other signaling pathways lead to myocyte dysfunction and cell death. Increased collagen production results in progressive cardiac fibrosis. Progressive myocardial dysfunction and remodeling are the natural history of untreated myocardial disease.

Treatment

Nonpharmacologic Treatment

For adequate treatment of dilated cardiomyopathy, precipitating factors must be identified and addressed. Nonpharmacologic treatment is crucial and includes sodium and fluid restriction, alcohol avoidance, daily weight monitoring with a weight-loss action plan, and regular aerobic exercise. Ongoing patient and family education and regular outpatient follow-up reduce heart failure exacerbations, emergency department visits, and hospitalizations.

KEY FACTS

- ✓ Dilated cardiomyopathy—in many patients the cause is genetic, and up to 30% of patients with dilated cardiomyopathy have at least 1 identifiable affected family member
- ✓ Atrial and ventricular arrhythmias—common in dilated cardiomyopathy
- ✓ After diagnosis of dilated cardiomyopathy—treatable secondary causes of LV dysfunction should be sought
- ✓ In severe coronary artery disease—reversible LV dysfunction can be caused by hibernating myocardium. With revascularization, LV dysfunction may improve gradually
- ✓ Substantial hibernating myocardium—identification of affected patients is difficult; reference standard is positron emission tomography to evaluate metabolic activity

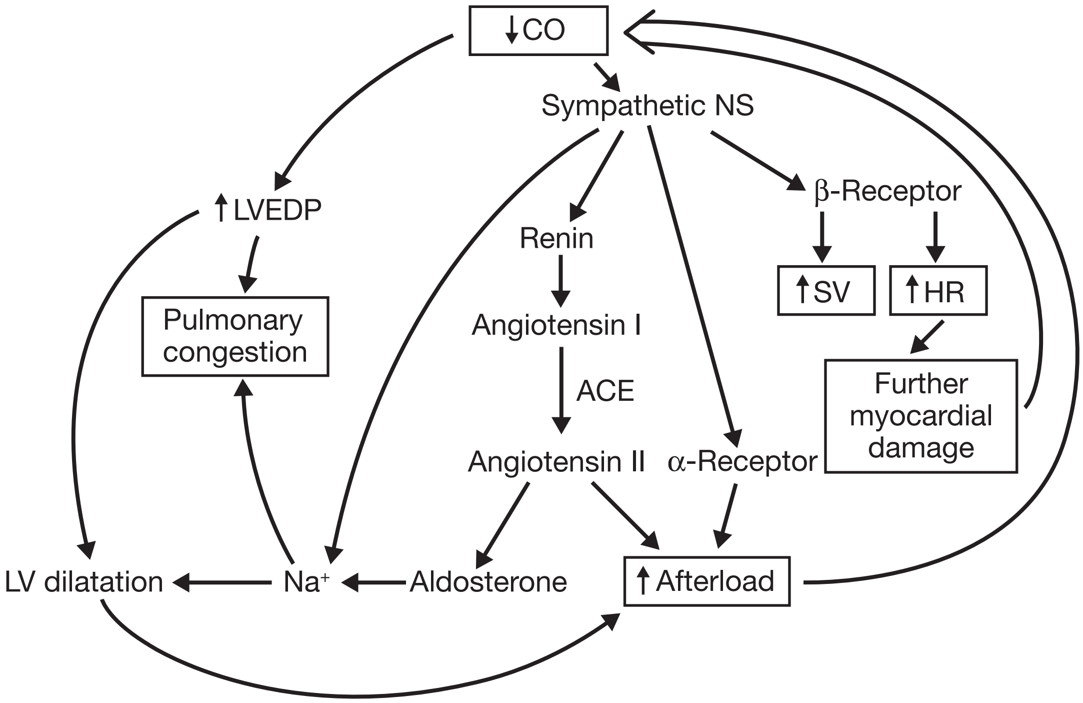

Figure 6.4. *Neurohormonal Response to Decreased Myocardial Contractility. ACE indicates angiotensin-converting enzyme; CO, cardiac output; HR, heart rate; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; Na*$^+$*, sodium ion; NS, nervous system; SV, stroke volume.*

Pharmacologic Treatment

The mainstays of pharmacologic therapy are ACE inhibitors, β-adrenergic blockers, and diuretics. ACE inhibitors decrease afterload, decrease sodium retention by inhibiting aldosterone formation, and directly affect myocyte growth and myocardial remodeling (Figure 6.5).

ACE inhibitors provide symptomatic improvement in patients with NYHA functional class II to IV failure and improve mortality rate in patients with moderate and severe heart failure. In asymptomatic patients, ACE inhibitors prevent onset of heart failure and reduce the need for hospitalization. The dose of the ACE inhibitor should be titrated up as tolerated on the basis of symptoms and blood pressure. Upward dose adjustment as tolerated is beneficial even in clinically compensated patients receiving low to intermediate doses. Common adverse effects include hypotension, hyperkalemia, azotemia, cough, angioedema (mild or severe), and dysgeusia. The benefits and potential adverse effects of ACE inhibitors are thought to be a class effect.

Angiotensin II receptor blockers provide hemodynamic benefits similar to those of ACE inhibitors in patients with dilated cardiomyopathy. They can be used in patients who have cough and angioedema with use of ACE inhibitors because they do not inhibit the breakdown of bradykinin (the cause of cough and angioedema). They are less beneficial than ACE inhibitors in the reverse remodeling of the myocardium, and thus they remain second-line treatment.

β-Adrenergic blockers (β-blockers) improve symptoms and ejection fraction and decrease hospitalizations and death in patients with systolic heart failure. They may have unwanted hemodynamic effects in the acute setting (eg, negative inotropic effects, attenuation of heart rate response that may be maintaining cardiac output in the clinical setting of reduced stroke volume), but they provide long-term benefit by modifying the unfavorable biologic effects of enhanced adrenergic tone. This benefit may take up to 6 months to observe. These drugs are most useful for patients with asymptomatic LV dysfunction after myocardial infarction and NYHA class II or III symptoms. They can be given cautiously to patients with class IV symptoms but should *not* be given to patients with substantial volume overload and cardiogenic shock. Initial dosing should be low, with close clinical follow-up. Upward titration of the β-blocker dose should be slow and cautious. Critically, the likelihood of patients continuing treatment with β-blockers is much higher when treatment is initiated during a hospitalization for heart failure. Well-studied β-blockers with established benefit for patients with heart failure include metoprolol succinate, carvedilol, and bisoprolol.

Diuretics are part of the routine management when symptoms and signs of systemic and pulmonary congestion are present. Diuretic doses should be minimized when possible because of associated neurohormonal activation and electrolyte imbalance. Fluid overload can be treated initially with thiazide or loop

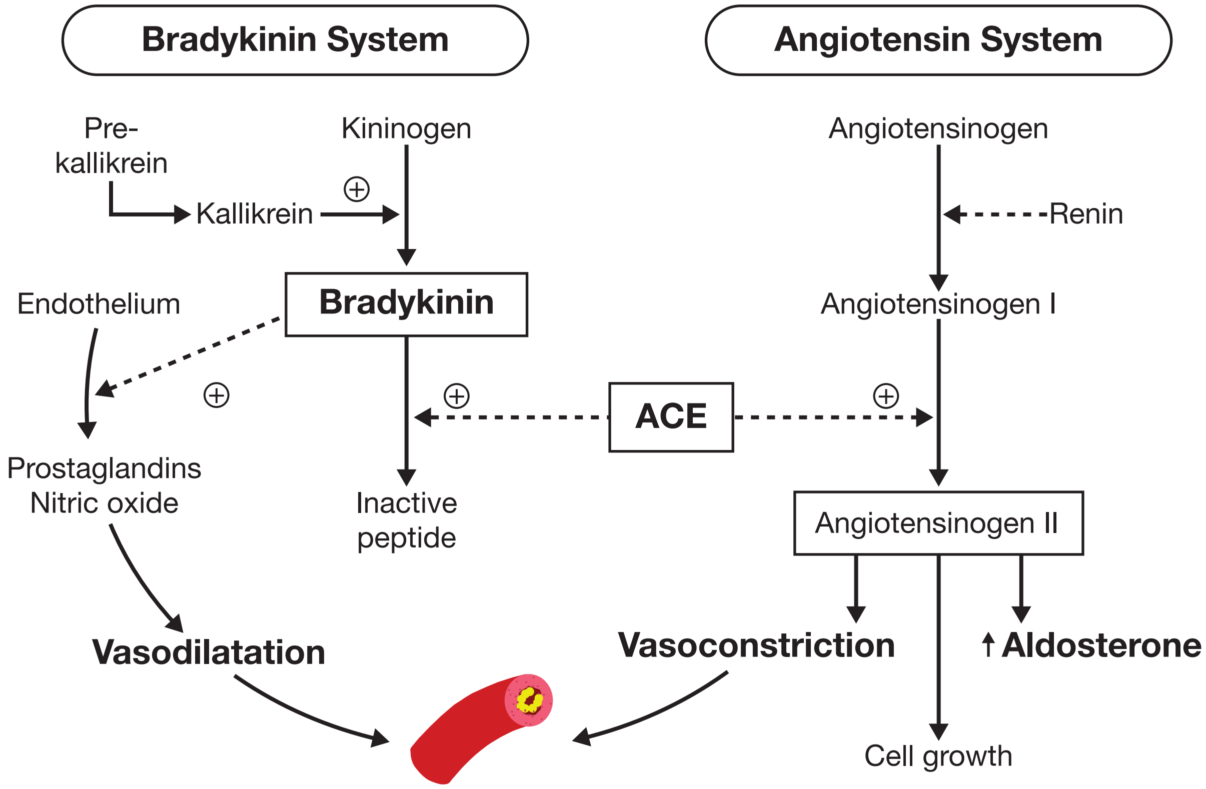

Figure 6.5. Action of ACE on the Bradykinin and Angiotensin Systems. ACE indicates angiotensin-converting enzyme.

diuretics. Occasionally, a combination of thiazides and loop diuretics is needed for severe fluid retention. The addition of spironolactone can help in patients with hypokalemia and may provide additional benefit by blocking aldosterone-mediated effects.

Drugs directly affecting myocardial contractility include digoxin, phosphodiesterase inhibitors (milrinone), and β-agonists (dopamine and dobutamine). Digoxin provides symptomatic relief when the ejection fraction is less than 40%, but it does not improve survival. It is useful for ventricular rate control and atrial fibrillation and for patients who are symptomatic despite treatment with ACE inhibitors and β-blockers. Because digoxin is excreted by the kidneys, dosage must be decreased in older patients and patients with renal dysfunction. Because of drug-drug interactions, digoxin dosage should be decreased with concomitant administration of amiodarone, verapamil, and quinidine. Short-term use of parenteral inotropic agents (milrinone and dobutamine) may improve symptoms, but long-term use *increases* the mortality rate, and therefore these drugs should be used transiently in the hospital for low-output states and occasionally for palliative purposes in refractory end-stage heart failure.

Aldosterone antagonists may provide additional benefit by inhibiting fibrosis and combating mechanical and electrical remodeling. Significant survival benefit has been shown in patients with NYHA class III to IV heart failure. Eplerenone, a selective aldosterone inhibitor, provides survival benefit at 30 days and 1 year in patients who have had infarction and who have LV dysfunction and either heart failure or diabetes mellitus. However, use of aldosterone antagonists has considerable risk of hyperkalemia. Thus, they must be given carefully with cautious follow-up, avoidance of nonsteroidal anti-inflammatory drugs, and prompt attention to illnesses predisposing to dehydration.

High-dose nitrates and hydralazine in combination provide symptomatic improvement and improved mortality rate in patients with heart failure, but this approach is inferior to ACE inhibitors when used alone. It is used in patients who are unable to tolerate ACE inhibitors or angiotensin receptor blockers because of renal insufficiency or hyperkalemia. The combination has been shown to increase survival in African American patients when given as adjunctive therapy to ACE inhibitors and β-blockers.

Amlodipine and felodipine are safe in patients with dilated cardiomyopathy. They can be used to treat hypertension that persists despite optimal dosages of ACE inhibitors and β-blockers, but they do not provide a survival benefit. First-generation calcium channel blockers (eg, verapamil, diltiazem, nifedipine) are *contraindicated* because of their negative inotropic effects.

Anticoagulation with warfarin therapy is recommended for patients in atrial fibrillation and those with intracardiac thrombus or a history of systemic or pulmonary thromboembolism, but it is not recommended as prophylaxis in the clinical setting of ventricular dysfunction. Retrospective studies have suggested that aspirin may diminish the benefits of ACE inhibitors by blocking prostaglandin-induced vasodilatation. An increased incidence of hospitalizations for heart failure was also observed in patients with dilated cardiomyopathy receiving aspirin. The most common recommendation is to use low-dose aspirin therapy in heart failure and coronary artery disease.

Device Therapy

Implanted defibrillators improve survival when used at least 40 days after a myocardial infarction in patients with ischemic and nonischemic dilated cardiomyopathies who have ejection fractions less than 35% despite optimal medical therapy. They should be offered to patients who have a reasonable functional status with at least 1 year of survival. Patients in sinus rhythm with ventricular dyssynchrony may benefit from biventricular pacing (cardiac resynchronization therapy). Current defibrillator implantation criteria are sinus rhythm, QRS duration more than 120 milliseconds, NYHA class III to IV, ejection fraction less than 35%, and optimal medical management. Cardiac resynchronization therapy results in improvement in symptoms, exercise capacity, LV ejection fraction, and survival in well-selected patients.

Cardiac Replacement Therapy

Heart transplant is the procedure of choice for patients with dilated cardiomyopathy and severe refractory symptoms. With a successful transplant, the 1-year survival rate can exceed 90%. Early referral to a heart transplant center is recommended for patients with refractory heart failure. Long-term complications include rejection, infection, hypertension, hyperlipidemia, malignancy, and accelerated coronary vasculopathy. Donor availability is the major limiting factor. In selected patients, LV assist devices have been approved by the US Food and Drug Administration and are used either as a bridge to transplant or as final (destination) therapy.

KEY FACTS

- ✓ Treatment of dilated cardiomyopathy—pharmacologic mainstays are ACE inhibitors, β-blockers, and diuretics
- ✓ Short-term use of parenteral inotropic agents in dilated cardiomyopathy—may improve symptoms, but long-term use *increases* the mortality rate; thus, these agents should be used transiently in the hospital for low-output states and occasionally palliatively in refractory end-stage heart failure
- ✓ Amlodipine and felodipine—safe to use for dilated cardiomyopathy; can be used to treat hypertension that persists despite use of ACE inhibitors and β-blockers, but amlodipine and felodipine do not provide a survival benefit
- ✓ First-generation calcium channel blockers—contraindicated for dilated cardiomyopathy because of their negative inotropic effects
- ✓ Aspirin use in dilated cardiomyopathy—may diminish effects of ACE inhibitors by blocking prostaglandin-induced vasodilatation; increased incidence of hospitalizations for heart failure has been found in patients receiving aspirin
- ✓ Current recommendation for aspirin use in dilated cardiomyopathy—use in patients with heart failure and coronary artery disease
- ✓ Heart transplant—procedure of choice for dilated cardiomyopathy with severe, refractory symptoms

Heart Failure With Preserved Ejection Fraction

Approximately one-half of hospitalized patients with newly diagnosed heart failure have a normal ejection fraction. Many of these patients have contractile abnormalities that could be identified by more sophisticated evaluation techniques, but ejection fraction is the most widely available measure of systolic function and continues to be the standard. Heart failure with preserved ejection fraction is a heterogeneous group of disorders and includes hypertrophic and restrictive cardiomyopathies, infiltrative cardiac disorders, and constrictive pericarditis.

Many patients have a history of hypertension. Some have fairly normal diastolic filling properties at rest, but exertional hypertension, ischemia, or both cause deterioration of diastolic filling properties, resulting in increased filling pressure. Others have abnormal baseline diastolic compliance with superimposed volume overload, which increases diastolic filling pressures. Other patients have exuberant heart rate responses to exercise with inadequate diastolic filling periods, and others rely on the atrial contribution to ventricular filling and have difficulty when atrial fibrillation develops. Some patients have low output due to severe regurgitant valve disease (including severe tricuspid regurgitation) or bradycardia. Severe occult renal insufficiency is also a common finding in this condition.

It is important to try to understand the mechanism of the diastolic dysfunction to tailor the most effective treatment, which might include some combination of antihypertensive or coronary revascularization strategies, diuretic treatment, ventricular rate slowing or support (pacemaker), restoration of sinus rhythm, valvular intervention, or renal replacement therapy. Morbidity and mortality rates in this group of patients are high, approaching the rates in patients with reduced ejection fraction and heart failure.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is a rare (approximately 0.2% prevalence in the general population) heterogeneous group of disorders characterized by increased thickness of the ventricle and preserved ejection fraction. The hypertrophy may be regional (involving the septum, mid left ventricle, or apex) or concentric. Obstruction may occur in the LV outflow tract or midventricular cavity. Diagnosis is based on increased myocardial wall thickness on echocardiography in the absence of an underlying cause such as hypertension, aortic stenosis, chronic renal failure, or infiltrative disease. Because of its hereditary nature, first-degree relatives of patients should be screened; genetic counseling is advised for patients considering childbearing.

Key Definition

Hypertrophic cardiomyopathy: *a rare heterogeneous group of disorders characterized by increased thickness of the ventricle and preserved ejection fraction.*

Symptoms

Hypertrophic cardiomyopathy appears to have a bimodal distribution of age at presentation. Affected boys and young men (typically, teenaged or in their early 20s) often present with syncope and sudden death. An X-linked variant known as *LAMP2* cardiomyopathy (also called *Danon disease*) has been described in young patients. Affected older patients (sixth and seventh decades of life) typically present with shortness of breath and angina and may have a better prognosis than young patients. The classic presentation in the younger group is a heart murmur or LV hypertrophy on ECG during physical examination of a young athlete. The classic presentation in the older group is pulmonary edema in an older woman after noncardiac surgery and worsening with diuresis, afterload reduction, and inotropic support (due to worsening dynamic LV outflow tract obstruction). The classic symptom triad is syncope, angina, and dyspnea. The symptoms are similar to those of valvular aortic stenosis.

The per-year frequency of evolution from hypertrophic to dilated cardiomyopathy is 1.5%. This percentage may reflect either the natural history or a superimposed secondary process such as ischemia. The treatment of a "burnt-out hypertrophic" condition is then the same as that of other dilated cardiomyopathies.

Pathophysiology

Signs and symptoms of hypertrophic cardiomyopathy are caused by 4 major abnormalities: diastolic dysfunction, LV outflow tract obstruction, mitral regurgitation, and ventricular arrhythmias. Diastolic dysfunction is caused by many mechanisms, including marked abnormalities in calcium metabolism (abnormal ventricular relaxation), high afterload due to LV tract obstruction (which also delays ventricular relaxation), and severe hypertrophy and increased muscle mass (decreased compliance). Diastolic dysfunction leads to increased LV diastolic pressure, angina, and dyspnea. Coronary microvascular dysfunction also contributes to angina and dyspnea. In many patients, dynamic LV tract obstruction is caused by the hypertrophied septum encroaching into the LV outflow tract. Subsequently, the anterior leaflet of the mitral valve is "sucked in" (systolic anterior motion), and LV outflow tract obstruction is created. Because of this pathophysiologic process, dynamic outflow tract obstruction increases dramatically with decreased preload, decreased afterload, or increased contractility.

Systolic anterior motion of the mitral valve distorts the mitral valve apparatus during systole and may cause considerable mitral regurgitation. Thus, the degree of mitral regurgitation is dynamically influenced by the degree of LV outflow tract obstruction. Patients with severe mitral regurgitation usually have severe symptoms of dyspnea. Cellular disorganization leads to abnormalities in the conduction system, and these patients are prone to ventricular arrhythmias. Frequent ventricular arrhythmias may cause sudden death or syncope.

LV outflow tract obstruction and mitral regurgitation are caused by distortion of the mitral valve apparatus (systolic anterior motion). They are dynamically influenced by preload, afterload, and contractility.

Examination

The carotid artery upstroke and LV impulse are abnormal in patients with hypertrophic cardiomyopathy. The carotid artery upstroke is more rapid than in aortic stenosis. If LV outflow tract obstruction is extensive, the carotid artery upstroke has a bifid quality. When LV hypertrophy is considerable, the LV impulse is sustained and there is often a palpable *a* wave. The first heart sound is normal, but the second heart sound is paradoxically split. Patients with excessive LV outflow tract obstruction may have a triple apical impulse and a loud systolic ejection murmur. The murmur changes in intensity with changes in loading conditions (Box 6.5). A holosystolic murmur of mitral regurgitation may be present; it increases in intensity with increases in the dynamic LV outflow tract obstruction.

Maneuvers affect the mitral regurgitant murmur of hypertrophic obstructive cardiomyopathy differently than other mitral regurgitant murmurs. When mitral regurgitation is *not* due to hypertrophic obstructive cardiomyopathy, the murmur increases with increasing afterload and varies little with changes in contractility and preload. When mitral regurgitation *is* due to hypertrophic cardiomyopathy, increased afterload decreases the dynamic LV outflow obstruction and thus the degree of mitral regurgitation. In patients with hypertrophic cardiomyopathy with obstruction, the intensity of the ejection murmur increases. The arterial pulse volume *decreases* on the beat following a premature ventricular contraction (the Brockenbrough sign) as a result of postectopic increased contractility and decreased afterload, resulting in more dynamic obstruction. These changes differ from those in patients with fixed LV outflow tract obstruction (eg, aortic stenosis), in whom *both* murmur intensity and pulse volume increase with the beat following a premature ventricular contraction.

Box 6.5 • Dynamic Left Ventricular Outflow Tract Obstruction

- Increased obstruction
  - Decreased afterload
    - Amyl nitrite
    - Vasodilators
  - Increased contractility
    - Postpremature ventricular contraction beat
    - Digoxin
    - Dopamine
  - Decreased preload
    - Squat-to-stand positioning
    - Nitrates
    - Diuretics
    - Valsalva maneuver (strain phase)
- Decreased obstruction
  - Increased afterload
    - Handgrip
    - Stand-to-squat positioning
  - Decreased contractility
    - β-Adrenergic blockers
    - Verapamil
    - Disopyramide
  - Increased preload
    - Fluids

Diagnostic Testing

A marked LV hypertrophy pattern on ECG (Figure 6.6) is usually seen in patients with hypertrophic cardiomyopathy. By comparison, patients with apical hypertrophy have deep, symmetrical T-wave inversions across the precordium (Figure 6.7). ECG abnormalities may precede echocardiographic abnormalities; thus, surveillance echocardiography is appropriate in patients with suspicious ECG results.

Echocardiography shows severe hypertrophy of the myocardium (LV wall thickness >16 mm in diastole) with no other identified cause. Hypertrophy may be in any part of the myocardium. Doppler echocardiography can be used to diagnose LV outflow tract obstruction, measure its severity, and detect mitral regurgitation. Cardiac catheterization is no longer necessary to diagnose dynamic LV outflow tract obstruction.

Patients with hypertrophic cardiomyopathy may have sudden death. Because of the strong association between ventricular arrhythmias and sudden death, 48- to 72-hour Holter monitoring is recommended for all patients with hypertrophic cardiomyopathy. Predictors of sudden death include a family history of sudden death or a personal or family history of severe LV hypertrophy, ventricular tachycardia on Holter monitoring or electrophysiologic study, and history of syncope. Genetic markers may identify patients with a strong propensity for sudden death. In some patients, carefully supervised stress testing may be indicated to search for induced ventricular tachycardia, to determine exercise tolerance, and to evaluate the variables contributing to symptoms.

Treatment

Symptomatic Patients

For symptomatic patients, initial treatment is with drugs that decrease contractility, in an attempt to decrease LV outflow tract obstruction (Figure 6.8). The most effective medication is a high dose of β-blocker (equivalent of >240 mg propranolol per day). Although verapamil may be used if β-adrenergic blockade fails, it may cause sudden hemodynamic deterioration in patients with high resting LV outflow tract gradients because of its vasodilating properties. Disopyramide may improve symptoms by decreasing LV outflow tract obstruction, but anticholinergic adverse effects limit its use. All drugs that reduce afterload or preload and those that increase contractility *must* be avoided in patients with hypertrophic cardiomyopathy. Diuretics may be cautiously used for volume-overloaded states.

Asymptomatic Patients

Asymptomatic patients should be assessed for risk of sudden cardiac death. Treatment of asymptomatic nonsustained ventricular tachycardia is controversial (Figure 6.9). No antiarrhythmic agent is uniformly effective, and any agent may make the arrhythmia worse. In selected patients with multiple risk factors for sudden death, empirical implantation of a cardiac defibrillator may be chosen. In patients who have had an out-of-hospital cardiac arrest, the treatment of choice is an implantable cardiac defibrillator.

KEY FACTS

- ✓ Heart failure with preserved ejection fraction—about one-half of hospitalized patients with newly diagnosed heart failure have normal ejection fraction
- ✓ Hypertrophic cardiomyopathy—affected boys and young men often present with syncope and sudden death
- ✓ ECG findings in hypertrophic cardiomyopathy—marked LV hypertrophy pattern is usually seen (deep, asymmetrical T-wave inversions across the precordium are seen in apical hypertrophy)
- ✓ ECG abnormalities in hypertrophic cardiomyopathy—may precede echocardiographic abnormalities, and thus surveillance echocardiography is appropriate in patients with suspicious ECG results
- ✓ Recommendation for all patients with hypertrophic cardiomyopathy—affected patients may have sudden death; because of the strong association between ventricular arrhythmias and sudden death, 48- to 72-hour Holter monitoring is recommended

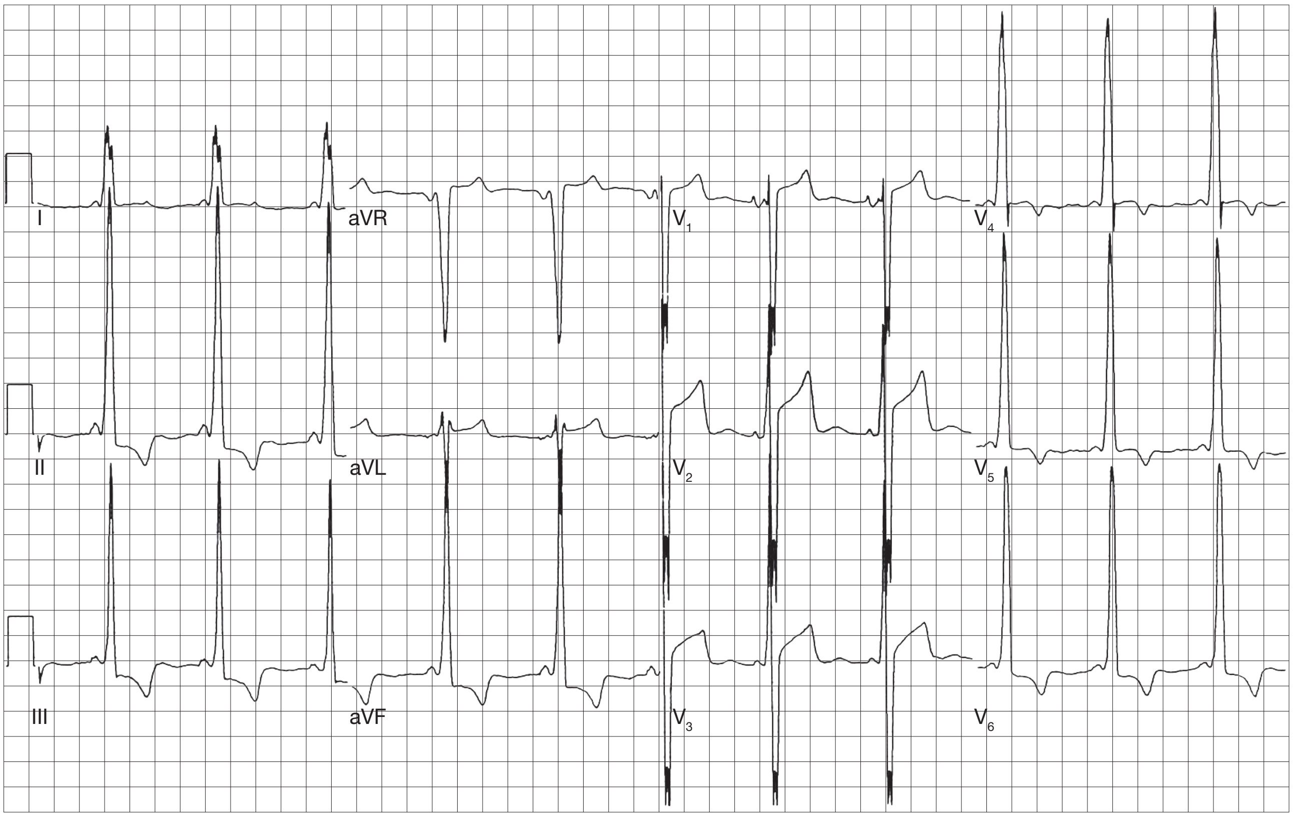
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6

Figure 6.6. *Electrocardiogram in Hypertrophic Cardiomyopathy. Marked left ventricular hypertrophy is noted.*

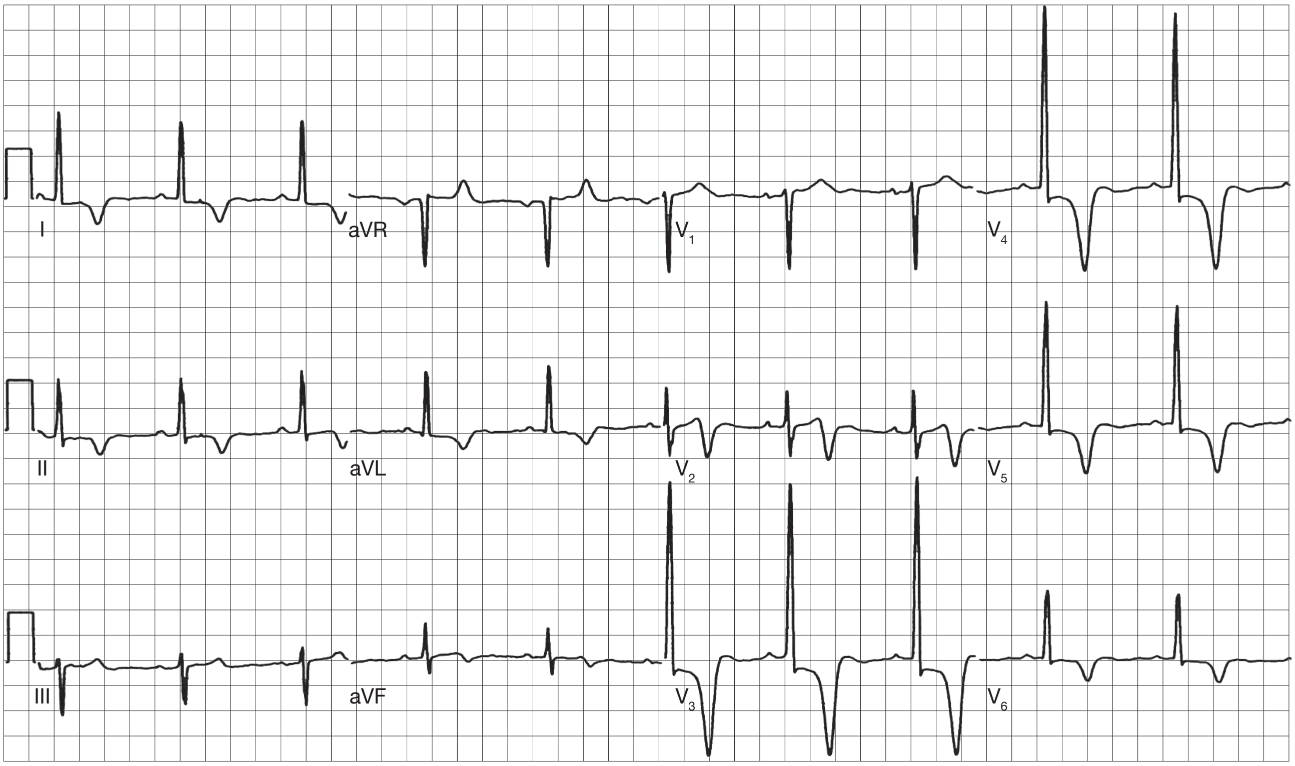
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6

Figure 6.7. *Electrocardiogram in Apical Hypertrophic Cardiomyopathy. Deep symmetrical T-wave inversions are shown in precordial leads.*

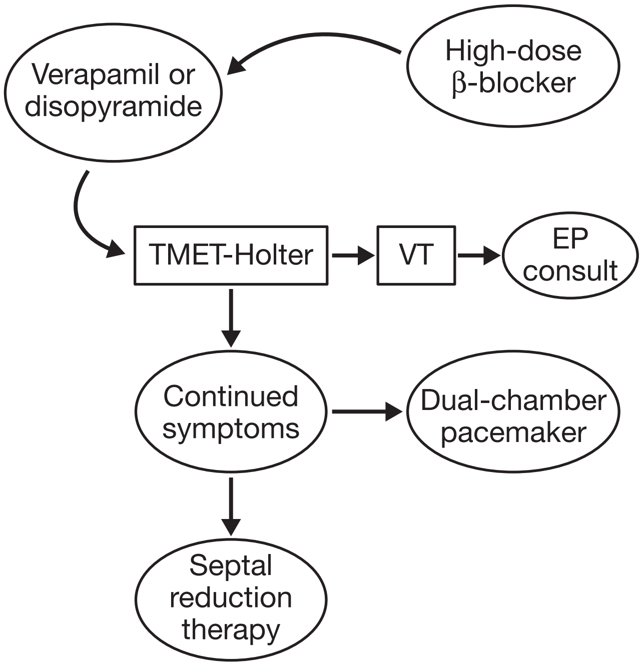

Figure 6.8. *Treatment of Symptomatic Hypertrophic Cardiomyopathy. EP indicates electrophysiologic; TMET, treadmill exercise test; VT, ventricular tachycardia.*

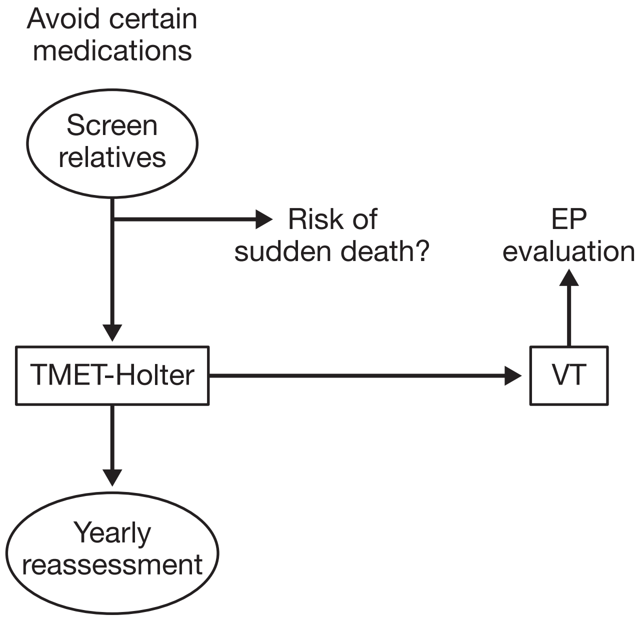

Figure 6.9. *Treatment of Asymptomatic Hypertrophic Cardiomyopathy. EP indicates electrophysiologic; TMET, treadmill exercise test; VT, ventricular tachycardia.*

Restrictive Cardiomyopathy

Diastolic dysfunction is the primary abnormality in restrictive cardiomyopathy and is usually due to abnormal relaxation, abnormal ventricular filling, and ineffectual atrial contribution to filling, which in turn affect pulmonary and systemic circulations, causing shortness of breath and edema. In addition, because the ventricle cannot fill adequately to meet its preload requirements, low cardiac output (called *Starling mechanism*), fatigue, and lethargy result. Normal or near-normal LV ejection fraction and volumes are present in most patients with restrictive cardiomyopathy.

The cause of primary restrictive cardiomyopathy is unknown. The 2 major categories are idiopathic restrictive cardiomyopathy and endomyocardial fibrosis. Progressive fibrosis of the myocardium occurs in idiopathic restrictive cardiomyopathy. Familial cases, often with associated peripheral myopathy, have been reported. Endomyocardial fibrosis is probably an end stage of eosinophilic syndromes in which there is intracavitary thrombus filling of the left ventricle. This fibrosis restricts filling and causes increased diastolic pressures. Fibrosis also may involve the mitral valve, causing severe mitral regurgitation. Two different forms of endomyocardial fibrosis may exist: active inflammatory eosinophilic myocarditis (temperate climate zones) and chronic endomyocardial fibrosis (tropical climate zones).

Infiltration diseases involving the myocardium (eg, amyloidosis) have a presentation and pathophysiology similar to those of primary restrictive cardiomyopathy. Signs and symptoms similar to those of restrictive cardiomyopathy also may develop after radiation therapy and anthracycline chemotherapy. Although other infiltrative diseases (eg, sarcoidosis, hemochromatosis) initially may mimic restrictive cardiomyopathy, they usually progress to a dilated cardiomyopathy by the time they cause cardiac symptoms.

Signs and Symptoms

Patients with restrictive cardiomyopathy usually present with symptoms of right heart failure, such as edema, dyspnea, and ascites. Atrial arrhythmias due to passive atrial enlargement are frequently present, and the patient may present with atrial fibrillation. Jugular venous pressure is almost always increased, with rapid x and y descents. The precordium is quiet and heart sounds are soft. There may be an apical systolic murmur of mitral regurgitation and a left sternal border murmur of tricuspid regurgitation. A third heart sound may be present. Dullness at the bases of the lungs is consistent with bilateral pleural effusions. ECG usually shows low or normal voltage with atrial arrhythmias. Chest radiography may show pleural effusions with a normal cardiac silhouette or atrial enlargement.

Diagnosis

Restrictive cardiomyopathy is diagnosed with echocardiography. Typical findings are normal LV cavity size, preserved ejection fraction, and marked biatrial enlargement. In right heart failure, the inferior vena cava is enlarged. In amyloid heart disease, echocardiography shows thickened myocardium with a scintillating appearance, a pericardial effusion, and thickened regurgitant valves. In endomyocardial fibrosis, an apical thrombus (without underlying apical akinesis) or thickening of the endocardium under the mitral valve occurs, which often tethers the valve, causing mitral regurgitation. Other causes of restrictive cardiomyopathy have nonspecific echocardiographic features. Cardiac catheterization shows increase and end-equalization of all end-diastolic pressures. A typical "square-root sign" or "dip-and-plateau" pattern is present, consistent with early rapid filling. Endomyocardial biopsy usually is not helpful except to confirm the diagnosis of amyloidosis.

Treatment

Treatment of idiopathic restrictive cardiomyopathy is usually symptom based. Diuretics decrease filling pressures and give symptomatic relief, but these effects may be at the expense of further decreases in cardiac output. Heart transplant is the only proven therapy for patients with severe restrictive cardiomyopathy. Corticosteroids are appropriate during the early stages of eosinophilic endocarditis. Endomyocardial fibrosis can be surgically resected and the mitral valve can be replaced, although the mortality rate is significant.

Differentiation of restrictive cardiomyopathy from constrictive pericarditis is important. Both have similar presentations and findings on clinical examination and diagnostic studies. However, in constrictive pericarditis, pericardiectomy produces symptomatic improvement and, frequently, survival. Therefore, exploratory thoracotomy may be indicated in patients with normal LV systolic function, large atria, and severe increase of diastolic filling pressures if doubt remains after anatomical imaging (computed tomography or magnetic resonance imaging) and other tests (eg, echocardiography, cardiac catheterization).

KEY FACTS

- ✓ Severe restrictive cardiomyopathy—heart transplant is the only proven therapy
- ✓ Restrictive cardiomyopathy and constrictive pericarditis—differentiation of these 2 conditions is important. They have similar presentations and findings on clinical examination and diagnostic studies, but in constrictive pericarditis, pericardiectomy produces symptomatic improvement and, frequently, survival

7

Hypertension[a]

C. SCOTT COLLINS, MD; CHRISTOPHER M. WITTICH, MD, PharmD

Definition

Hypertension is the most common condition seen in primary care. It can lead to myocardial infarction, stroke, renal failure, and death if not adequately treated. Normal blood pressure is defined as less than 120/80 mm Hg (Table 7.1), according to the 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Elevated blood pressure is defined as 120 to 129/less than 80 mm Hg. Stage 1 hypertension is a blood pressure of 130 to 139/80 to 89 mm Hg; stage 2, 140 or more/90 or more mm Hg.

Initial Evaluation

Initial evaluation of hypertension should focus on 1) determining the contributing lifestyle and genetic risk factors, 2) ordering basic laboratory tests, 3) identifying and treating secondary causes of hypertension, and 4) identifying target organ damage.

Lifestyle and Individual Risk Factors

Lifestyle risk factors include family history of hypertension, black race, obesity, physical inactivity, excess sodium and alcohol intake, dyslipidemia, and type A personality traits.

Basic Laboratory Testing

Laboratory testing in the initial evaluation of hypertension is aimed at looking for end-organ damage. This should include complete blood cell count; urinalysis; analysis of glucose, creatinine, and electrolyte levels; lipid profile; and electrocardiography.

Secondary Causes of Hypertension

Diseases that cause secondary hypertension and key features of each condition are listed in Table 7.2. Physical examination and history should be tailored to ruling out these diseases.

Target Organ Damage

Target organ damage can occur as a result of hypertension (Table 7.3). Organs typically involved include heart, brain, kidney, arteries, and eyes. Physical examination should focus on these organs, looking for signs of heart failure, vascular disease, and retinopathy.

Treatment

Goals of Treatment

The goal of antihypertensive therapy is to eliminate the morbidity and death caused by disease attributable to long-term hypertension. Blood pressure treatment targets for adults aged 18 years or older have been defined in the 2017 ACC/AHA/American Academy of Physician Assistants/Association of Black Cardiologists/American College of Preventive Medicine/American Geriatrics Society/American Pharmacists Association/American Society of Hypertension/American Society for Preventive Cardiology/National Medical Association/Preventive Cardiovascular Nurses Association Guideline for the Prevention, Detection, Evaluation, and

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[a] Portions of this chapter have been published in Whelton PK, Carey RM, Aronow WS, Casey DR Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018 Jun; 71(6):e13-115. Erratum in: Hypertension. 2018 Jun; 71(6):e140-4; used with permission.

Table 7.1 • Categories of BP in Adults*

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120-129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130-139 mm Hg	or	80-99 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

Abbreviations: BP, blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in Section 4 [of original source]); DBP, diastolic blood pressure; and SBP systolic blood pressure.

* Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.

From Whelton PK, Carey RM, Aronow WS, Casey DR Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2017 Nov 13. pii: HYP.0000000000000065. [Epub ahead of print]; used with permission.

Table 7.2 • Secondary Causes of HTN

Cause	Key Features
Endocrine	
Pheochromocytoma	Presents with headaches, diaphoresis, and palpitations If appropriate, screen with plasma metanephrine value
Primary aldosteronism	Presents with hypokalemia and HTN If appropriate, screen with aldosterone to renin ratio
Cushing disease	Presents with hyperglycemia, hypokalemia, and HTN If appropriate, screen with 24-hour urinary cortisol value
Hyperparathyroidism	Screen with serum calcium value
Hypothyroidism	Presents with diastolic HTN
Cardiac	
Coarctation of aorta	Examine for weak, delayed, or absent femoral pulse Rib notching on chest radiography
Obstructive sleep apnea	Presents in overweight persons with loud snoring, large neck circumference, morning headaches, and daytime sleepiness Confirm diagnosis with polysomnography
Renal	
Renal artery stenosis	Presents in smokers, persons with CAD or with new-onset HTN after age 50 years Examine for high-pitched systolic-diastolic abdominal bruit
Fibromuscular dysplasia	Presents in women, usually younger than 30 years without family history of HTN
Renal parenchymal disease	Check creatinine value and results of urinalysis

Abbreviations: CAD, coronary artery disease; HTN, hypertension.

Data from Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003 Dec;42(6):1206-52. Epub 2003 Dec 1.

Management of High Blood Pressure in Adults. The hypertension management algorithm from this report defines blood pressure thresholds at which to initiate lifestyle or pharmacologic interventions and parameters for follow-up (Figure 7.1). A blood pressure target of less than 130/80 mm Hg is recommended for adults with confirmed hypertension and known cardiovascular disease. This target also is relevant for adults who have a 10% or higher 10-year atherosclerotic cardiovascular disease (ASCVD) event risk, defined by the ACC/AHA Pooled Cohort Equations. The recommendation is based on high-quality evidence. For adults with confirmed hypertension without additional markers of increased cardiovascular disease risk, a blood pressure target of less than 130/80 mm Hg may be reasonable, but this level is based on lower-quality evidence.

Lifestyle Modification

Lifestyle modifications (Table 7.4) are essential for any patient found to have increased blood pressure or any stage of hypertension. The modifications may be sufficient as initial therapy for some persons. They are adjunctive therapy for persons with persistent hypertension and should be continued throughout hypertension management.

Pharmacologic Treatment

The 2017 High Blood Pressure Clinical Practice Guideline recommends initiation of medication therapy in patients for whom lifestyle modifications are inadequate or who have increased ASCVD risk, clinical ASCVD, or stage 2 hypertension. Initial medication recommendations are based on age, race, compelling indications, and diabetes mellitus or chronic kidney disease (CKD) status.

In the general hypertensive population, nonblack patients and diabetic patients without CKD should begin a treatment of thiazide diuretic, angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker, or calcium channel blocker, alone or in combination, as initial therapy. Black patients with or without diabetes mellitus and without CKD should be given a thiazide diuretic or calcium channel blocker alone or in combination as initial therapy. All patients, regardless of race, who have CKD should receive an ACE inhibitor or angiotensin receptor

Table 7.3 • Hypertensive Target Organ Injury

Target Organ	Injury	Clinical Marker/ Diagnosis
Heart	Left ventricular hypertrophy	S_4 gallop, forceful and prolonged apical thrust Displacement of point of maximal intensity Chest radiography, ECG, echocardiography
	Angina Prior myocardial infarction Prior revascularization	
	Heart failure (systolic or diastolic)	History, ECG History Lung rales S_3 gallop Edema Chest radiography, echocardiography
Brain	Stroke	History
	Leukoaraiosis	CT or MRI
	Dementia	History Cognitive testing
Kidney	Chronic kidney disease	Creatinine, serum urea nitrogen, urinalysis, eGFR
Arteries	Peripheral artery disease	History of claudication Bruits Diminished pulses
Eye	Retinopathy	Funduscopic examination: generalized and focal arteriolar narrowing “Copper wiring” of arterioles Arteriovenous nicking Cotton-wool spots Microaneurysms and macroaneurysms Flame- and blot-shaped retinal hemorrhages Retinal vein occlusion Optic disc swelling

Abbreviations: CT, computed tomography; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging; S_3, third heart sound; S_4, fourth heart sound.

blocker as initial therapy alone or in combination with another drug class. Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended for adults with stage 2 hypertension and an average blood pressure that exceeds 20/10 mm Hg above their blood pressure target. Adults initiating a new or adjusted drug regimen for hypertension should have a follow-up evaluation of adherence and response to treatment at monthly intervals until control is achieved.

KEY FACTS

- ✓ Hypertension—most common condition seen in primary care; can lead to myocardial infarction, stroke, renal failure, and death if not adequately treated
- ✓ Target organ damage in hypertension—typically involves heart, brain, kidneys, arteries, and eyes
- ✓ Treatment of hypertension—blood pressure goal for adults in the general population age <60 years is <140/90 mm Hg; for adults age ≥60 years, <150/90 mm Hg. Adults of all ages with diabetes mellitus and CKD have a blood pressure goal of <140/90 mm Hg
- ✓ Treatment of hypertension—nonblack patients and diabetic patients without CKD should start therapy with a thiazide diuretic, ACE inhibitor, angiotensin receptor blocker, or calcium channel blocker, alone or in combination, as initial therapy
- ✓ Treatment of hypertension—black patients with or without diabetes and without CKD should be given a thiazide diuretic or calcium channel blocker, alone or in combination, as initial therapy

Secondary Hypertension

Secondary causes of hypertension should be considered when the age at onset is unusual, when blood pressure changes suddenly, and when hypertension is refractory to treatment.

Renovascular Hypertension

Renovascular hypertension is a potentially curable form of secondary hypertension. Generally, renovascular hypertension is grouped into 1) renal artery stenosis and 2) fibromuscular dysplasia.

Clues that suggest renovascular hypertension include lack of a family history of hypertension, onset of hypertension before age 30 years (consideration of fibromuscular dysplasia is appropriate, especially in white women), and onset of hypertension after age 50 years (consideration of atherosclerotic renovascular disease is appropriate, especially in a smoker or a person with coronary or peripheral arterial disease). Another clue is presentation with accelerated hypertension.

The most important physical finding is an abdominal bruit, especially a high-pitched systolic-diastolic bruit in the upper abdomen or flank. However, 50% of persons with renovascular hypertension do not have this finding.

Options for the management of renovascular hypertension include interventional therapies when feasible and medical therapy for persons who are not candidates for an intervention procedure. Percutaneous transluminal angioplasty is the treatment

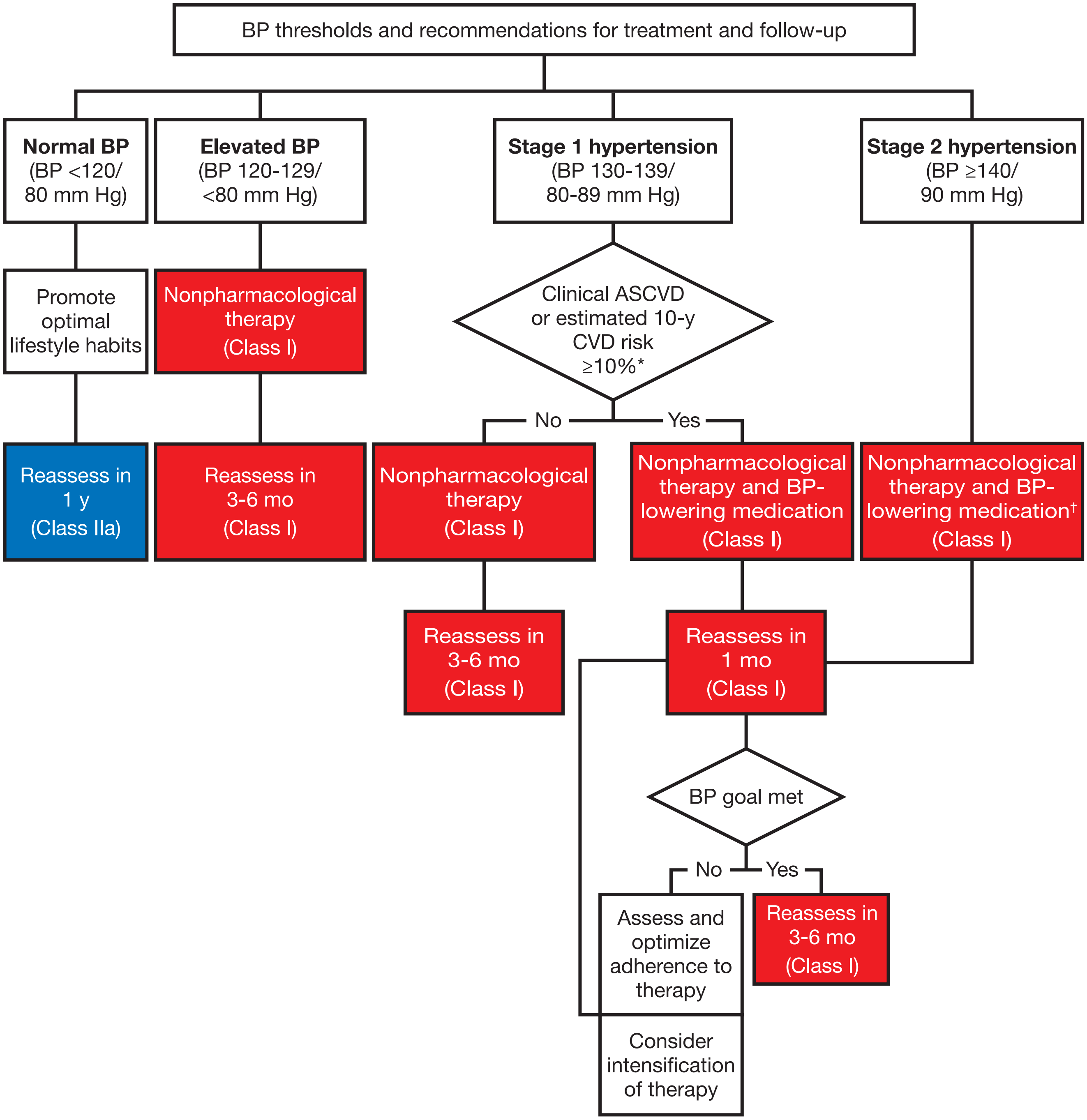
BP thresholds and recommendations for treatment and follow-up
Normal BP (BP <120/ 80 mm Hg)
Elevated BP (BP 120-129/ <80 mm Hg)
Stage 1 hypertension (BP 130-139/ 80-89 mm Hg)
Stage 2 hypertension (BP ≥140/ 90 mm Hg)
Promote optimal lifestyle habits
Nonpharmacological therapy (Class I)
Clinical ASCVD or estimated 10-y CVD risk ≥10%*
No
Yes
Reassess in 1 y (Class IIa)
Reassess in 3-6 mo (Class I)
Nonpharmacological therapy (Class I)
Nonpharmacological therapy and BP-lowering medication (Class I)
Nonpharmacological therapy and BP-lowering medication† (Class I)
Reassess in 3-6 mo (Class I)
Reassess in 1 mo (Class I)
BP goal met
No
Yes
Assess and optimize adherence to therapy
Reassess in 3-6 mo (Class I)
Consider intensification of therapy

Figure 7.1. *Hypertension Management Algorithm of the 2017 High BP Clinical Practice Guideline. ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; CVD, coronary artery disease. Applying the class of recommendation and level of evidence to clinical strategies, interventions, treatments, or diagnostic testing, the class (strength) of recommendations is indicated by color. Red indicates Class I (strong); blue, Class IIa (moderate). Further detail can be found in Table 1 of the original source. * Using the American College of Cardiology/American Heart Association Pooled Cohort Equations (Circulation. 2014 Jun 24;129[25 Suppl 2]:S1-45). Of note, patients with diabetes mellitus or chronic kidney disease are automatically placed in the high-risk category. After initiation of renin-angiotensin system inhibitor or diuretic therapy, assess blood tests for electrolytes and renal function at 2 to 4 weeks. † Consider initiation of pharmacologic therapy for stage 2 hypertension with 2 antihypertensive agents of different classes. Patients with stage 2 hypertension and BP ≥160/100 mm Hg should be promptly treated, carefully monitored, and subject to upward medication dose adjustment as necessary to control BP. Reassessment includes BP measurement, detection of orthostatic hypotension in selected patients (eg, older age, postural symptoms), identification of* white coat hypertension *or a* white coat effect, *documentation of adherence, monitoring of response to therapy, reinforcement of the importance of adherence, reinforcement of the importance of treatment, and assistance with treatment to achieve BP target.*

(From Whelton PK, Carey RM, Aronow WS, Casey DR Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2017 Nov 13. pii: HYP.0000000000000065. [Epub ahead of print]; used with permission.)

Table 7.4 • Lifestyle Modifications to Prevent and Manage Hypertension[*]

Modification	Recommendation	Approximate SBP Reduction (Range)[†]
Weight reduction	Maintain normal body weight (body mass index 18.5-24.9 kg/m^2).	5-20 mm Hg/10 kg
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat.	8-14 mm Hg
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride).	2-8 mm Hg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 minutes per day, most days of the week).	4-9 mm Hg
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks (eg, 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men and to no more than 1 drink per day in women and lighter-weight persons.	2-4 mm Hg

Abbreviation: DASH, Dietary Approaches to Stop Hypertension.

[*] For overall cardiovascular risk reduction, stop smoking.

[†] The effects of implementing these modifications are dose- and time-dependent and could be greater for some individuals.

From Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003 Dec;42(6):1206-52. Epub 2003 Dec 1; used with permission.

of choice for amenable lesions caused by fibromuscular dysplasia and is an option in some cases of atherosclerotic renovascular disease. The medical treatment of renovascular hypertension is the same as that of essential hypertension.

Renal Parenchymal Disease

Renal parenchymal disease is a common secondary cause of hypertension. The major mechanisms of hypertension in renal disease include volume expansion from impaired renal elimination of salt and water, over secretion of renin, and decreased production of renal vasodilators. ACE inhibitors and angiotensin receptor blockers reduce proteinuria and high glomerular transcapillary pressures, slowing further loss of renal function. However, these medications can cause hyperkalemia and an acute decline in renal function. Modest acute decreases in renal function (<30%) should be tolerated because they are often followed by stabilization and preservation of renal function. Calcium channel blockers are effective blood pressure–lowering agents in persons with CKD. Of note, nondihydropyridine calcium channel blockers reduce proteinuria, but dihydropyridine calcium channel blockers do not.

Primary Aldosteronism

The syndrome of primary aldosteronism is characterized by overproduction of aldosterone by the adrenal glands, leading to hypertension, hypokalemia, alkalosis, hyperglycemia, and increased aldosterone levels. Prevalence estimates range from 2% to 15% of the hypertensive population.

Primary aldosteronism should be suspected in hypertensive patients who have spontaneous hypokalemia or marked hypokalemia precipitated by usual doses of diuretics. However, in many patients with primary aldosteronism, the potassium level is normal. In addition, it should be suspected in patients with an adrenal mass, a history of early-onset hypertension, or a first-degree relative who has primary aldosteronism.

Screening for primary aldosteronism is done through the use of the aldosterone to renin ratio. This ratio should be measured when the patient is not taking an aldosterone-blocking medication. In essential hypertension, the average value of the ratio is 5.5. A ratio more than 15 to 20 suggests the diagnosis of primary aldosteronism.

Treatment of primary aldosteronism can involve spironolactone, eplerenone, other antihypertensive medications, or surgery.

Pheochromocytoma

Pheochromocytoma is a tumor that causes hypertension due to excess catecholamines. Pheochromocytoma is rare; its incidence is 2 to 8 cases per 1 million persons per year. The prevalence is 0.5% among persons with hypertension.

A *rule of 10* describes the typical locations of pheochromocytomas. The rule cites that 10% are extra-adrenal; 10% of extra-adrenal gland tumors are extra-abdominal; 10% occur in children; 10% are multiple or bilateral; 10% recur after the initial resection; 10% are malignant; 10% are found in persons without hypertension; and 10% are familial.

Patients can present with paroxysms of hypertension, but most have sustained hypertension. Paroxysms can be associated with headache, diaphoresis, and palpitations. The presentation of pheochromocytoma corresponds to 5 P's: *p*ressure, *p*ain, *p*alpitations, *p*erspiration, and *p*allor. Patients can also present with symptoms mimicking an anxiety attack. In addition, pheochromocytoma can be discovered as an incidental adrenal mass on an imaging study.

Pheochromocytoma is associated with numerous outcomes. They are multiple endocrine neoplasia 2A (medullary thyroid carcinoma, pheochromocytoma, and parathyroid tumors), multiple endocrine neoplasia 2B (medullary thyroid cancer, pheochromocytoma, and neuroma), neurofibromatosis, von Hippel-Lindau disease (pheochromocytoma, retinal hemangiomatosis, cerebellar hemangioblastomas, epididymal cystadenoma, renal and pancreatic cysts, and renal cell carcinoma), and familial paraganglioma syndrome.

Diagnosis of pheochromocytoma consists of biochemical confirmation with 24-hour urine collection to measure fractionated metanephrines and fractionated catecholamines. It involves blood testing to measure plasma levels of fractionated metanephrines.

Computed tomography or magnetic resonance imaging of the abdomen and pelvis is the initial test to locate a tumor after biochemical testing has confirmed the presence of the disorder. Treatment is surgical removal. Preoperatively, administration of a phenoxybenzamine is needed to control blood pressure and cardiac rhythm. Because pheochromocytomas can recur in 10% of cases, long-term biochemical follow-up is required.

Coarctation of the Aorta

Coarctation of the aorta is a constriction of the vessel usually immediately beyond the takeoff of the left subclavian artery. It is typically detected in childhood when blood pressure in the upper extremities is increased and blood pressure in the lower extremities is decreased. Weak or delayed lower-extremity pulses can also be present. Patients can have signs of lower-extremity claudication. Dilated collateral vessels can cause bruits and characteristic rib notching on chest radiography. Treatment is surgical repair.

Obstructive Sleep Apnea

Obstructive sleep apnea is associated with hypertension that may be severe and resistant to control. Upper body obesity is a risk factor for obstructive sleep apnea and is common in hypertensive persons. The diagnosis of obstructive sleep apnea should be considered in persons who are overweight, snore loudly, have a large neck circumference, and report morning headaches and daytime sleepiness.

Other Causes of Hypertension

Cushing syndrome should be considered in the hypertensive person who has impaired fasting glucose and unexplained hypokalemia.

Hypothyroidism is associated with diastolic hypertension due to decreased cardiac output and contractility. Tissue perfusion is maintained by an increase in peripheral vascular resistance mediated by increased activity of the sympathetic nervous system.

Hyperparathyroidism may increase blood pressure directly through hypercalcemia, which increases peripheral vascular resistance, and indirectly by increasing vascular sensitivity to catecholamines.

KEY FACTS

- ✓ Clues suggestive of renovascular hypertension—lack of family history of hypertension, onset of hypertension before age 30 years (consideration of fibromuscular dysplasia is appropriate, especially in white women), onset of hypertension after age 50 years (consideration of atherosclerotic renovascular disease, especially in a smoker or a person with coronary or peripheral arterial disease), or presentation with accelerated hypertension
- ✓ Primary aldosteronism—should be suspected in hypertensive patients who have spontaneous hypokalemia or marked hypokalemia precipitated by usual doses of diuretics
- ✓ Pheochromocytoma—presentation corresponds to 5 P's: *p*ressure, *p*ain, *p*alpitations, *p*erspiration, and *p*allor

Special Cases of Hypertension

Pregnancy

Blood pressure typically decreases early in pregnancy (in the first 16-18 weeks) and then gradually increases. Hypertension during pregnancy is defined as a systolic blood pressure of 140 mm Hg or greater *or* a diastolic blood pressure of 90 mm Hg or greater on 2 separate occasions. Hypertension during pregnancy is associated with increased neonatal morbidity and mortality rates.

Preeclampsia is defined as a blood pressure greater than 140/90 mm Hg and proteinuria (24-hour urine protein excretion >0.3 g) that develops after the 20th week of gestation. Eclampsia is defined by seizures that occur in the presence of preeclampsia and cannot be attributed to other causes. Patients with preeclampsia can also have headache, blurry vision, epigastric pain, nephrotic-range proteinuria (>3.5 g in 24 hours), oliguria, creatinine level greater than 1.2 mg/dL, low platelet count, evidence of microangiopathic hemolytic anemia (abnormal blood smear results or increased lactate dehydrogenase value), increased liver transaminase values, and pulmonary edema.

Key Definition

Preeclampsia: *blood pressure >140/90 mm Hg and proteinuria (24-hour urine protein excretion >0.3 g) that develop after the 20th week of gestation.*

The HELLP syndrome (*h*emolysis, *el*evated *l*iver enzymes, and *l*ow *p*latelet count) occurs when intravascular coagulation and liver ischemia develop in preeclampsia. This syndrome can rapidly develop into a life-threatening disorder of liver failure and worsening thrombocytopenia in the presence of only mild or moderate hypertension. The most serious complication of the HELLP syndrome is liver rupture, which is associated with high maternal and fetal mortality rates.

Hypertensive Crisis

Hypertensive crisis is defined as a systolic blood pressure less than 180 mm Hg, a diastolic blood pressure less than 120 mm Hg, or both. It can be subdivided into hypertensive urgency and emergency.

Hypertensive urgency is severe hypertension without evidence of acute target organ injury. It should be treated to decrease blood pressure to safer levels over 24 to 48 hours. This decrease can usually be achieved in the outpatient setting with oral agents.

Hypertensive emergency is severe hypertension with evidence of acute injury to target organs. It implies the need for hospitalization in the intensive care setting to immediately lower blood pressure with parenteral therapy. Parenteral medications such as sodium nitroprusside, nitroglycerin, clevidipine, nicardipine, fenoldopam, labetalol, esmolol, hydralazine, enalaprilat, and phentolamine are the available drugs of choice for hypertensive emergencies.

Key Definitions

Hypertensive urgency: *severe hypertension without evidence of acute target organ injury.*

Hypertensive emergency: *severe hypertension with evidence of acute injury to target organs.*

8 Ischemic Heart Disease[a]

NANDAN S. ANAVEKAR, MB, BCH

Ischemic heart disease results from diminished myocardial blood supply and its attendant clinicopathologic manifestations. It may be clinically silent or present with syndromes categorized as stable angina, unstable angina, non–ST-elevation acute coronary syndrome (NSTE-ACS), ST-elevation myocardial infarction (MI), or sudden death. Ischemic heart disease causes nearly 800,000 deaths annually in the United States. Notably, about one-third of deaths annually in the United States are due to MI. Primary prevention and new treatments have led to a substantial decrease in death from acute MI since 1970 (Figure 8.1).

Key Definition

Ischemic heart disease: *cardiac disease that results in diminished myocardial blood supply and its attendant clinicopathologic manifestations.*

Prevention

The atherosclerotic cardiovascular disease (ASCVD) risk calculator is the most commonly used model to calculate the 10-year risk of ischemic heart disease http://professional.heart.org/professional/GuidelinesStatements/PreventionGuidelines/UCM_457698_Prevention-Guidelines.jsp (Circulation. 2014 Jun 24;129[25 Suppl 2]:S49-73). The score is derived from prespecified risk factors: age, sex, race, total cholesterol, high-density lipoprotein cholesterol (HDL-C), systolic blood pressure, blood pressure–lowering medication use, diabetes status, and smoking status.

The risk factors for which interventions have been proven to reduce cardiac events include tobacco use, serum low-density lipoprotein cholesterol (LDL-C) level, serum HDL-C level, and hypertension (Box 8.1). Factors that clearly increase the risk of ischemic heart disease and for which therapeutic interventions are likely to be effective include diabetes mellitus, physical inactivity, obesity, metabolic syndrome, and serum triglyceride levels. Factors for which intervention may improve subsequent risk include psychosocial factors (eg, anxiety, depression).

Smoking more than doubles the risk of ischemic heart disease and increases *mortality* risk by 50%. The relative risk in smokers who quit smoking decreases rapidly, approaching the level in nonsmokers within 2 to 3 years. Plasma levels of total cholesterol and LDL-C are important risk factors for ischemic heart disease. A 1% decrease in total serum cholesterol reduces risk by 2% to 3%. Lowering the LDL-C level slows progression and may result in regression of coronary atherosclerosis. Lowering the LDL-C level also prevents coronary events, possibly because of atherosclerotic plaque stabilization.

Hypertension is an important modifiable risk factor for coronary artery disease. Traditionally, the goal of antihypertensive therapy is the prevention of atherosclerotic cardiovascular and renal complications. In a review of several thousand patients with hypertension treated before 1990, mainly with diuretics or β-adrenergic blockers (β-blockers) for a mean duration of 5 years, a reduction in systolic blood pressure of 10 to 12 mm Hg or in diastolic blood pressure of 5 to 6 mm Hg resulted in a decrease in incidences of stroke of 35% to 40%; coronary

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[a] Portions of this chapter have been published in Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 24;129(25 Suppl 2):S1-45. Epub 2013 Nov 12. Erratum in: Circulation. 2014 Jun 24;129(25 Suppl 2):S46-8; used with permission.

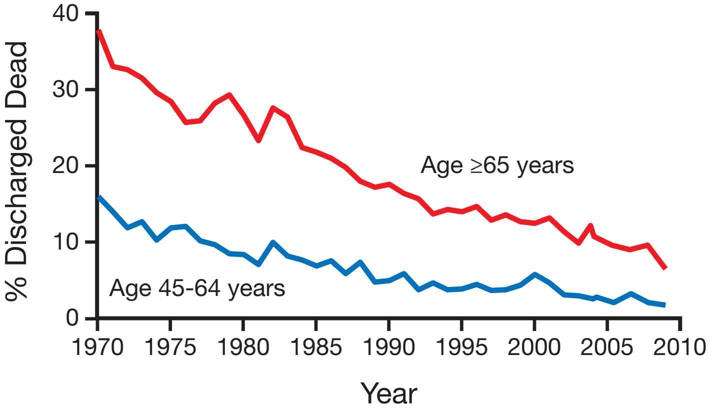

Figure 8.1. *Case-Fatality Rate for Acute Myocardial Infarction in the United States, 1970-2009.*
(Data from National Heart, Lung, and Blood Institute. Morbidity and mortality: 2012 chart book on cardiovascular, lung, and blood diseases. Bethesda [MD]: National Institutes of Health; updated 2012. [cited 2019 Jan 4]. Available from: https://www.nhlbi.nih.gov/files/docs/research/2012_ChartBook_508.pdf.)

artery disease, 20% to 25%; congestive heart failure, 45% to 55%; and cardiovascular death, 20% to 25% (Lancet. 1999 Feb 20;353[9153]:611-6).

The risk of MI is decreased 35% to 55% with maintenance of an active vs a sedentary lifestyle. Adjusted mortality rates for ischemic heart disease are 2 to 3 times higher in men and 3 to 7 times higher in women with diabetes mellitus than in men and women without diabetes. Heavy alcohol use increases the risk of ischemic heart disease, but moderate consumption decreases risk. Metabolic syndrome is present in 20% of the US population, and it is associated with a 2-fold to 3-fold increase in deaths from cardiovascular disease. Aspirin is recommended for persons at intermediate risk for ischemic heart disease and at low risk for bleeding. This recommendation includes patients with an absolute risk of more than 15% over 10 years by Framingham score or patients with diabetes with a risk of more than 10% over 10 years. The role of aspirin in the primary prevention of stroke or overall cardiovascular death is uncertain. Estrogen replacement therapy is *not* indicated for women with cardiovascular disease, and it may be harmful.

Secondary prevention aims to prevent recurrent ischemic events in patients with known ischemic heart disease. Smoking cessation and optimum treatment of hyperlipidemia, hypertension, and diabetes mellitus are essential. Statins reduce ischemic events after MI more than would be expected from their effect on atherosclerosis progression alone, possibly because of stabilization of lipid-rich, rupture-prone plaques. Statins decrease the overall mortality rate by 30% and the coronary event–related mortality rate by 42% in patients with a prior MI and a high total cholesterol level (>220 mg/dL). Statins reduce the risk of

Box 8.1 • Risk Factors for Ischemic Heart Disease

Modifiable Factor	**Nonmodifiable Factor**	**Novel Factor**
Increased LDL-C level	Age	Inflammatory markers (eg, C-reactive protein)
Low HDL-C level	Male sex	Small, dense LDL
Cigarette smoking	Family history of premature CAD[a]	Lipoprotein(a)
Hypertension		Homocysteine
Diabetes mellitus		Fibrinogen
Sedentary lifestyle		
Obesity		
Metabolic syndrome		
Stress and depression		
Socioeconomic factors		

Abbreviations: CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol.

[a] Age at onset <55 years in men and <65 years for primary relatives.

fatal heart disease or recurrent MI by 24% in patients with a prior MI and average levels of cholesterol.

The clinical indications for cholesterol-lowering therapies were radically revised in the most recent American College of Cardiology/American Heart Association clinical guidelines (2013); the most striking changes were related to the dismissal of LDL-C and non–HDL-C target levels. Instead, the evidence-based recommendation has been focused on the groups of patients who would benefit from pharmacologic therapies and the categorization of therapies as high, moderate, or low intensity, depending on the proportion of decrease in LDL-C with therapy. The pharmacologic treatment emphasizes statins as the mainstay of lipid-lowering therapies. With regard to the intensity of therapy, rather than focusing on cutoff targets for cholesterol levels, the current recommendations highlight high-intensity therapy as that which decreases LDL-C by more than 50%; moderate-intensity therapy as that which decreases LDL-C by 30% to 50%, and low-intensity therapy as that which decreases LDL-C by less than 30%. These recommendations formulate 4 groups of patients who are deemed to benefit from lipid-lowering, specifically statin, therapy (Box 8.2).

Currently, no evidence-based recommendations are available for or against specific LDL-C or non–HDL-C targets for primary or secondary prevention of atherosclerotic cardiovascular disease. For secondary prevention, high-intensity statin therapy should be initiated or continued as first-line therapy for women and men age 75 years or younger who have clinical atherosclerotic heart disease, unless contraindicated. A moderate-intensity regimen may be reasonable for persons older than 75 years or who cannot tolerate the high-intensity regimen. For primary prevention in persons age 21 years or older with an LDL-C level of 190 mg/dL or more, statin therapy is indicated and a high-intensity regimen or maximal tolerated dose is recommended, unless otherwise contraindicated. After maximum statin therapy has been achieved, addition of a nonstatin drug may be considered to further lower the LDL-C level, after evaluation of the potential for atherosclerotic cardiovascular disease risk-reduction benefits, adverse effects, and drug-drug interactions and after consideration of patient preferences. For patients age 40 to 75 years who have diabetes mellitus and an LDL-C level of 70 to 189 mg/dL, moderate-intensity statin therapy should be initiated or continued. A high-intensity regimen is reasonable in patients with a 7.5% or greater estimated 10-year risk of atherosclerotic heart disease. In adults with diabetes who are younger than 40 years or older than 75 years, it is reasonable to evaluate the potential for atherosclerotic cardiovascular disease benefits, adverse effects, and drug-drug interactions and to consider patient preferences.

Lifestyle changes, including a low-fat, low-cholesterol diet, weight management, and physical activity, are essential for cholesterol lowering and continue to be in the background of management superimposed with the pharmacologic strategies mentioned above. Soluble fiber (10-25 g/day) and plant stanols or sterols (2 g/day) should be considered as therapeutic options.

Novel risk factors proposed for ischemic heart disease, especially for patients who do not have the conventional risk factors, include increased blood levels of lipoprotein(a); homocysteine; small, dense LDL particle (phenotype B); and fibrinogen. In addition, acute and chronic inflammation and possibly lifetime exposure to pathogens (eg, *Chlamydia*, cytomegalovirus, *Helicobacter*) have been proposed as potential factors in the pathogenesis of atherosclerosis.

Box 8.2 • Characteristics of 4 Patient Groups That Can Benefit From Lipid-Lowering Treatment

1. Clinical atherosclerotic disease as defined by a prior history of myocardial infarction, stable or unstable angina, history of coronary or other arterial revascularization, stroke or transient ischemic attack, or atherosclerotic peripheral vascular disease
2. Age 21 years or older with primary increases in low-density lipoprotein cholesterol (LDL-C) to 190 mg/dL or more
3. Age 40 to 75 years with diabetes mellitus but without clinical atherosclerotic disease and an LDL-C level of 70 to 189 mg/dL
4. Age 40 to 75 years without atherosclerotic disease or diabetes mellitus but with an LDL-C level of 70 to 189 mg/dL and an estimated 10-year risk of atherosclerotic heart disease of 7.5% or more

KEY FACTS

- ✓ Ischemic heart disease—causes nearly 800,000 deaths annually
- ✓ MI—accounts for about one-third of deaths annually in the United States
- ✓ Smoking—more than doubles the risk of ischemic heart disease and increases mortality risk by 50%
- ✓ Relative risk of ischemic heart disease in smokers who quit smoking—decreases rapidly and approaches the level in nonsmokers within 2 to 3 years
- ✓ Statins—
  - reduce ischemic events after MI more than would be expected from their effect on atherosclerosis progression alone, possibly because of stabilization of lipid-rich, rupture-prone plaques
  - decrease overall death by 30% and coronary event-related death by 42% in patients with a prior MI and a high cholesterol level (>220 mg/dL)
  - reduce the risk of fatal heart disease or recurrent MI by 24% in patients with a prior MI and average levels of cholesterol (total cholesterol, <240 mg/dL; LDL-C, >125 mg/dL)

Chronic Stable Angina

Pathophysiologic Factors

A mismatch between myocardial oxygen demand and supply causes myocardial ischemia. Demand is determined by heart rate, contractility, and wall stress (determined by afterload and preload).

Normally, coronary blood flow can increase up to 5 times to meet effort-related increases in myocardial oxygen demands. The double product (heart rate × systolic blood pressure) is a useful index for quantifying myocardial oxygen demand. Ischemia occurs when flow reserve is inadequate, usually the result of fixed coronary artery disease.

Restriction of resting blood flow sufficient to cause resting ischemia does not occur unless vessel stenosis is more than 95%. However, decreased overall flow reserve begins to occur at about 60% vessel stenosis, and symptoms of exercise-induced ischemia may begin. The temporal sequence of events during ischemia is diastolic dysfunction→regional wall motion abnormalities→electrocardiography (ECG) changes→pain.

Clinical Presentation

Symptomatic Chronic Stable Coronary Artery Disease

Typical angina is characterized by retrosternal pain that occurs with cardiovascular stress and is relieved with rest or relieved with nitroglycerin therapy. Atypical angina is defined by the presence of only 2 of these 3 features. Noncardiac chest pain is defined as the presence of 1 or none of these features.

Angina may be precipitated by any activity that increases myocardial oxygen consumption. The pain or discomfort has various descriptions, such as pressure, burning, stabbing, ache, hurt, or heaviness, or it may be described as only shortness of breath. It can be substernal or epigastric, and it may radiate to the neck, jaw, shoulder, back, elbow, or wrist. In stable angina, the pain lasts 2 to 30 minutes and is usually relieved by rest. Findings that may accompany ischemia include a fourth heart sound and mitral regurgitant murmur due to papillary muscle dysfunction. ST-segment depression may be found on ECG, indicating subendocardial ischemia.

Silent Ischemia

Silent ischemia is defined as the presence of dynamic ST-segment depression in the absence of symptoms. It can occur with chronic stable coronary artery disease, with unstable angina, or after MI. Patients with diabetes mellitus may have silent ischemia, possibly due to neuropathy. It is also more common in elderly patients. Medical therapy is similar to that for symptomatic ischemia. Unknown is whether percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) should be performed for silent ischemia in the absence of other markers of high risk. The prognosis for this condition is the same as for symptomatic ischemia.

Key Definition

Silent ischemia: *the presence of dynamic ST-segment depression in the absence of symptoms.*

Testing in Ischemic Heart Disease

Ancillary testing for ischemic heart disease is strongly imaging-based and focuses on cardiac performance at rest and with stress, whether physical or chemically induced. The gold standard assessment for coronary artery disease continues to be invasive coronary angiography. Imaging studies commonly used in the evaluation of patients with ischemic heart disease include the following.

Electrocardiography

This study is inexpensive and is performed at the bedside. It assesses underlying rhythm. Voltage changes may indicate the presence of ventricular hypertrophy, and dynamic ST-segment changes may point to the presence of underlying ischemic heart disease. ECG may be coupled with an exercise stress test to assess for dynamic ST-segment changes that may indicate stress-induced ischemia. The stress ECG is positive for ischemia when there is a flat or downsloping ST-segment depression of 1 mm or more with exertion, whereas it is uninterpretable when there is more than 1 mm of *resting* ST-segment depression, left bundle branch block, left ventricular hypertrophy, paced rhythm, or preexcitation (Wolff-Parkinson-White syndrome). Digoxin therapy results in an uninterpretable stress ECG.

Chest Radiography

This study is useful to gauge cardiac size and pulmonary vascular markings, which may be prominent in congestive heart disease.

Echocardiography

Typically, transthoracic echocardiography is the mainstay of cardiac function in the evaluation of ischemic heart disease. A resting study provides information regarding cardiac structure and function, including valve function. In the appropriate clinical setting, echocardiography may also be coupled with either physical or chemical stress to assess for stress-induced ischemia.

Nuclear Cardiac Stress Testing

This test uses either physical or chemical stress to assess for changes in myocardial perfusion, comparing resting vs stress perfusion images. It can reliably evaluate for prior MI, active ischemia, and the presence of viable myocardium in the clinical setting of coronary artery disease associated with profound ventricular dysfunction.

Cardiac Magnetic Resonance Imaging

This study allows assessment of both cardiac structure and function. Its unique ability to characterize tissue inflammation allows for quantification of myocardial scar and viability. Stress cardiac magnetic resonance imaging is an emerging tool in cardiac imaging.

Cardiac Computed Tomography

This study has greatest power in coronary artery imaging. It is especially powerful in its negative predictive value. The coronary calcium score allows for further risk stratification of patients who are at intermediate risk for coronary events. It is also extremely useful for identifying coronary artery anomalies that may pose a risk of ischemia development, such as anomalies of origin or myocardial bridging. Computed tomography requires the use of an iodinated intravenous contrast agent. It is of limited value for patients with greater than mild-to-moderate coronary calcification or an irregular rhythm. These current limitations likely represent transient phenomena as computed tomography technology advances.

Left Heart Catheterization

This test involves access to the arterial side of the circulation with special catheters designed to engage the coronary ostia. The technique uses intra-arterial injection of iodinated contrast agent to delineate vascular structures. In addition, ventricular function can be assessed with direct left ventriculography. Although coronary angiography has limitations, it is the standard for defining the severity and extent of coronary artery disease. Subjective visual estimation of the percentage of stenosis may underestimate the severity of disease, especially when it is diffuse, because angiography outlines the vessel lumen. The risk of serious complications of coronary angiography is approximately 0.1%, including MI, stroke, and death. Patients with advanced age, severe left ventricular dysfunction, left main coronary artery disease, or other noncardiovascular comorbidities have a somewhat higher risk of complications. Other complications include vascular complications (0.5%) and contrast-medium nephropathy.

Risk Stratification by Stress Testing

Treadmill exercise testing can identify high-risk patients. Results that indicate high risk are listed in Box 8.3.

Patients who achieve a good workload with appropriate blood pressure and heart rate responses without marked ST-segment depression have an excellent prognosis. Therefore, medical management may be preferred for these patients.

Imaging-based stress testing slightly increases the sensitivity and specificity of ECG exercise testing. In nuclear perfusion imaging, a tracer is injected at peak exercise and labels areas of hypoperfusion as a defect or so-called cold spot. Scanning is repeated a few hours later at rest, and persistent cold spots indicate infarction, whereas reperfused spots indicate areas of inducible ischemia. In patients with left bundle branch block or severe left ventricular hypertrophy, thallium and sestamibi scanning can give false-positive results during exercise stress.

Box 8.3 • Treadmill Exercise Results Indicating High Risk of Ischemic Heart Disease

A positive electrocardiogram in stage I of the Bruce protocol or at a heart rate less than 120 beats per minute

ST-segment depression more than 2 mm

ST-segment depression more than 6 minutes in duration after stopping exercise

Decrease in blood pressure

Multiple perfusion or wall motion defects (>25% of segments with exercise) and an increase in left ventricular end-systolic volume with exercise

In exercise echocardiography, 2-dimensional echocardiography is performed at rest and at peak exercise. The test is positive for ischemia when new regional wall motion abnormalities develop, global systolic function decreases, or left ventricular end-systolic volume increases.

Stress testing should *not* be performed for patients with high-risk unstable angina, patients who have had acute MI in the prior 2 days, or patients with symptomatic severe aortic stenosis, uncontrolled heart failure, or uncontrolled arrhythmia. In these clinical settings, direct invasive angiography should be considered.

Imaging stress tests for diagnostic purposes are considerably more expensive than the basic ECG treadmill exercise test and should not be routinely used. Indications for imaging-based stress testing include when the patient is unable to exercise, the result of resting ECG is uninterpretable, the ECG result is possibly false-positive, or specific regions of ischemia need to be localized (for planning revascularization procedures).

Pharmacologic stress tests are used for patients who cannot exercise. These tests include the use of vasodilators such as adenosine and dipyridamole (to redistribute flow away from ischemic myocardium). The tests are generally performed with a perfusion agent such as thallium or sestamibi. Alternatively, dobutamine is used as a chronotropic and inotropic agent to increase myocardial oxygen demand, and imaging is performed typically with echocardiography.

Stress tests should not be used for the diagnosis of ischemic heart disease of patients at high or low risk. Stress testing is appropriate for patients at intermediate risk to rule in or rule out ischemia. The pretest probability of ischemic heart disease is estimated using the following criteria: age (men age >40 years and women >60 years), male sex, and symptom status (in decreasing order of risk: typical angina, atypical angina, noncardiac chest pain, and asymptomatic) (Table 8.1 and Figure 8.2).

Table 8.1 • Pretest Probability of Coronary Artery Disease by Age, Sex, and Symptoms[a]

		Symptoms			
Age, y	**Sex**	**Typical/Definite Angina Pectoris**	**Atypical/Probable Angina Pectoris**	**Nonanginal Chest Pain**	**None**
30-39	Male	Intermediate	Intermediate	Low	Very low
	Female	Intermediate	Very low	Very low	Very low
40-49	Male	High	Intermediate	Intermediate	Low
	Female	Intermediate	Low	Very low	Very low
50-59	Male	High	Intermediate	Intermediate	Low
	Female	Intermediate	Intermediate	Low	Very low
60-69	Male	High	Intermediate	Intermediate	Low
	Female	High	Intermediate	Intermediate	Low

[a] High indicates more than 90%; intermediate, 10% to 90%; low, less than 10%; very low, less than 5%.

Data from Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation. 2002 Oct 1;106(14):1883-92.

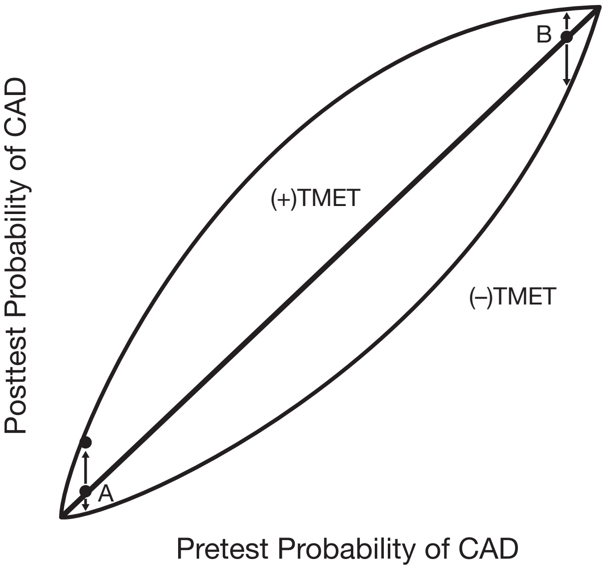

Figure 8.2. *The Effect of Bayes Theorem on the Ability of TMET to Diagnose CAD. Patient A is a young patient with atypical chest pain and no risk factors. Pretest probability of coronary artery disease is low (5%). If the test results are negative, the probability decreases to 3%. However, if the results are positive, the probability is less than 15%. Patient B is an older man with typical chest pain and multiple risk factors. Pretest probability of coronary artery disease is high (90%), and even with negative test results, the probability is higher than 70%. Thus, stress tests should not be used for the diagnosis of coronary artery disease in patients at high or low risk. CAD indicates coronary artery disease; TMET, treadmill exertion testing.*

KEY FACTS

- ✓ Coronary blood flow—normally can increase up to 5 times to meet effort-related increases in myocardial oxygen demands
- ✓ Double product (heart rate × systolic blood pressure)—useful index for quantifying myocardial oxygen demand
- ✓ Restriction of resting blood flow sufficient to cause resting ischemia—does not occur unless vessel stenosis is >95%. But decreased overall flow reserve begins to occur at about 60% vessel stenosis, and symptoms of exercise-induced ischemia may begin
- ✓ Temporal sequence of events during ischemia—diastolic dysfunction→regional wall motion abnormalities→ECG changes→pain
- ✓ Stress testing—should *not* be performed for patients with high-risk unstable angina, patients who have had acute MI in the prior 2 days, or patients with symptomatic severe aortic stenosis, uncontrolled heart failure, or uncontrolled arrhythmia

Medical Therapy for Angina

Medical therapy for chronic stable angina includes risk factor modification, antiplatelet therapy, and medication-based therapy of myocardial ischemia. Antiplatelet agents are essential. Aspirin reduces the likelihood of acute MI and death, but it does not prevent progression of atherosclerosis. Aspirin therapy provides greater benefit for secondary than for primary prevention. Treatable underlying factors that contribute to ischemia (eg, anemia, thyroid abnormalities, hypoxia) should always be sought.

A stepwise approach should be used when introducing a pharmacologic strategy to treat myocardial ischemia. Medications should be titrated according to symptoms. The dose of a first-line drug should be optimized before adding additional agents.

β-Blockers are the most effective and are first-line drugs for ischemic heart disease. They relieve angina by decreasing heart rate, reducing contractility, and decreasing afterload (blood pressure). They are the most effective drugs for reducing the double product (heart rate × blood pressure) with exercise. β-Blockers improve survival, especially of patients with prior MI or depressed left ventricular systolic function. They should not be used in the clinical setting of *marked* bronchospastic disease, decompensated heart failure, or bradycardia. However, β-blockers should be given to patients with left ventricular systolic dysfunction in the absence of overt heart failure. The target resting heart rate is 70 beats per minute or less, and the dose should be titrated to effect.

Nitrates should be added if symptoms continue despite optimal β-blocker therapy. Nitrates cause venodilatation and decreasing wall tension, thus relieving angina. Nitrate tolerance can develop with continuous exposure. Thus, a nitrate-free interval is important, particularly when using short-acting preparations. Sublingual nitroglycerin should be given to all symptomatic patients for use as needed.

Calcium channel blockers decrease afterload, heart rate, and contractility. Diltiazem and verapamil have more heart rate–lowering effects than the dihydropyridine group of calcium channel blockers and may be used when β-blockers are contraindicated. Short-acting calcium channel blockers, specifically the dihydropyridines (eg, amlodipine, nifedipine), may cause reflex tachycardia and increased mortality rate; therefore, they are relatively contraindicated for patients with ischemic heart disease. This detrimental effect probably does not occur with the longer-acting calcium channel blockers or in patients with normal systolic function, but these medications should be avoided in patients with left ventricular systolic dysfunction. If a calcium channel blocker is required for patients with left ventricular systolic dysfunction, amlodipine is preferred.

Ranolazine is a second-line drug used as an adjunct to one of the aforementioned drugs. Experience with its use is limited. Purported mechanism of action indicates an effect on membrane ion channels.

For patients with left ventricular dysfunction or nocturnal angina, diuretics and angiotensin-converting enzyme inhibitors decrease wall tension. They may be beneficial for secondary prevention in ischemic heart disease regardless of the degree of systolic function.

Percutaneous Coronary Intervention

PCI for chronic stable angina relieves symptoms but does not reduce the risk of MI or death. It is indicated for treatment of symptomatic patients, particularly those who remain symptomatic despite optimized medical therapy. An initial medical strategy is reasonable for most patients at low to moderate risk of an event (based on symptoms and the findings on stress testing or angiography). There is no clear role for PCI in management of asymptomatic disease.

PCI is performed at the time of coronary angiography. During percutaneous transluminal coronary angioplasty, the device is placed across a coronary stenosis and a balloon is inflated to increase the area of the lumen. This procedure "splits" the atheroma and stretches the vessel. The major problem is restenosis, occurring in 30% to 40% of patients within 6 months. Antiplatelet agents may decrease the rate of acute closure, but they do not prevent restenosis. Other catheter-based therapies such as atherectomy and laser have high restenosis rates and are infrequently used.

Intracoronary stent placement at the time of PCI decreases restenosis. Stents are used in approximately 90% of PCIs. The restenosis rate after successful bare-metal stent implantation is 20% to 30%. Stents also are used to treat acute complications of percutaneous transluminal coronary angioplasty such as acute dissection and have decreased the need for emergency CABG. However, for patients who have restenosis within a stent, the rate of recurrent restenosis is high (>60%) if another procedure is performed.

Drug-eluting stents are coated with and release drugs that considerably decrease restenosis (a decrease of 5%-10%). They are the most commonly used stents. They are associated with a higher risk of very late (>1 year) stent thrombosis than bare-metal stents. Newer (second-generation) drug-eluting stents have a much better thrombogenic profile than their predecessors and have markedly improved rates of stent thrombosis that equal or surpass those observed with bare-metal stents.

Dual antiplatelet therapy is initiated at the time of stent deployment, to prevent early restenosis. Duration varies according to the type of stent (Table 8.2). Recommendations regarding discontinuation of dual antiplatelet therapy for noncardiac surgery are outlined in Box 8.4.

The success rate for PCI is greater than 95%. Potential complications include MI (<5%), vascular complications (1%), emergency CABG (0.2%), and death (<0.5%). The risks of the procedure are higher during emergency procedures, in elderly patients, and in patients with severely reduced ejection fraction, acute coronary syndromes, or severe diffuse coronary artery disease.

PCI is the preferred revascularization strategy for single-vessel disease, young patients (age <50 years), elderly patients with serious comorbid conditions, and patients who are not surgical candidates.

Surgical Treatment

CABG uses the saphenous vein (occlusion rate of 20% at 1 year and 50% at 5 years) and the internal mammary artery (occlusion

Table 8.2 • Antiplatelet Therapy Used With Coronary Stents

Therapy	Duration
Aspirin	Indefinitely
Clopidogrel or prasugrel	At least 1 month for patient with stable disease
Bare-metal stent	At least 12 months for an acute coronary syndrome (unstable angina and myocardial infarction). If the risk of substantial bleeding outweighs the anticipated benefit, earlier discontinuation should be considered
Drug-eluting stent	12 months (a subset of patients may require long-term therapy). If the risk of morbidity because of bleeding outweighs the anticipated benefits afforded by thienopyridine therapy, earlier discontinuation should be considered

rate <10% at 10 years). CABG provides excellent symptom relief (partial relief in >90%, complete relief in >70%).

The indications for CABG (over medical therapy or PCI) are symptom relief for patients whose limiting symptoms are unresponsive to other management strategies and prolongation of life for patients with severe disease.

CABG improves the mortality rate of patients with severe disease, including left main coronary artery disease, 3-vessel disease with moderately depressed left ventricular function, 3-vessel disease with severe ischemic symptoms at a low workload, and multivessel disease with proximal left anterior descending artery involvement. In-hospital mortality rate after CABG varies widely (about 1% in most elective cases to 30% in high-risk cases). Mortality rate is increased with advanced age, female sex, reduced left ventricular function, diffuse multivessel disease, recent acute coronary syndrome, diabetes mellitus, repeat CABG, and emergency surgery. Complications of CABG include sternal wound infection (especially in patients with diabetes mellitus), severe left ventricular dysfunction (from perioperative MI or inadequate cardioprotection during cardiopulmonary bypass), and late constrictive pericarditis.

Box 8.4 • Treatment of Patients With Drug-Eluting Stents Who Need Noncardiac Surgery or an Invasive Procedure Within 1 Year of Percutaneous Coronary Intervention

Defer elective procedures for 1 year after stent placement and consider less invasive alternatives that may be performed for patients receiving dual antiplatelet therapy

Aspirin therapy must be continued during the perioperative period, unless absolutely contraindicated

Before urgent procedures, consideration should be given to performing them without discontinuation of dual antiplatelet therapy or with aspirin alone. The relative risks of perioperative bleeding vs stent thrombosis must be discussed with the surgical team. The risk of postoperative stent thrombosis is low, but it increases when use of 1 or both of the antiplatelet agents is discontinued. If stent thrombosis occurs, the associated morbidity and mortality rates are high

If clopidogrel therapy must be withheld for an urgent operation, withhold therapy for 5 days preoperatively. Ideally, clopidogrel therapy should be resumed with a 300-mg loading dose on the day of operation

Postcardiotomy Syndrome

Postcardiotomy syndrome occurs 2 weeks to 2 months postoperatively and consists of fever, pericarditis, and increased erythrocyte sedimentation rate. Rarely, it presents as pericardial tamponade. Postcardiotomy syndrome is likely an autoimmune process. Treatment is with aspirin, other nonsteroidal anti-inflammatory drugs, and colchicine. Rarely, constrictive pericarditis may be a late complication. The diagnosis should be suspected in patients presenting months to years after cardiac surgery with congestive heart failure and with predominantly right-sided signs of fluid overload, including increased jugular venous pressure but normal left ventricular ejection fraction.

Medical vs Catheter-Based vs Surgical Therapy

The decision about which therapy to use for a patient with chronic stable angina must be individualized. Factors to consider include disease severity, ischemia, symptoms, and the patient's age, lifestyle, and personal preference. The incidence of MI and emergency CABG with PCI is similar to that with medical management. PCI neither decreases risk of MI nor improves resting left ventricular function or survival. Procedure-related mortality rate is lower with PCI than with CABG.

More procedure-related infarctions and strokes occur with CABG than with PCI, and the duration of hospitalization is longer after CABG. The overall rates of death or MI at 5-year follow-up are similar for PCI and CABG (85%-90% free of death and 80% free of MI) except for patients with severe disease. This subgroup includes patients with left main coronary artery disease, 3-vessel disease with moderately depressed left ventricular function, 3-vessel disease with severe ischemic symptoms at a low workload, and multivessel disease with proximal left anterior descending artery involvement. CABG offers a survival benefit for these patients. Patients with multivessel or anatomically complex disease who have CABG have less angina, require less antianginal medication, and are less likely to need a repeat revascularization procedure. For patients with diabetes mellitus and diffuse multivessel disease, survival is greater with CABG than with PCI. Increased survival is related to having a patent internal mammary artery graft to the left anterior descending artery.

KEY FACTS

- ✓ β-Blockers—most effective agents and first-line drugs for ischemic heart disease
- ✓ β-Blockers—relieve angina by decreasing heart rate, reducing contractility, and decreasing afterload (blood pressure)
- ✓ PCI for chronic stable angina—relieves symptoms but does not reduce the risk of MI or death
- ✓ CABG—reduces risk of death for patients with severe disease, including left main coronary artery disease, 3-vessel disease with moderately depressed left ventricular function, 3-vessel disease with severe ischemic symptoms at a low workload, and multivessel disease with proximal left anterior descending artery involvement

Coronary Artery Spasm

The vasomotor tone of coronary arteries is important in the pathogenesis of coronary artery disease. Arterial injury leads to coronary artery vasoconstriction. The vascular endothelium regulates vasomotor tone by releasing relaxing factors (eg, prostacyclin, nitric oxide), thereby preventing vasoconstriction and platelet deposition. Endothelial dysfunction leads to depletion of these factors, and the coronary arteries become prone to spasm. Most clinical episodes of coronary artery spasm are superimposed on atherosclerotic plaques. However, coronary artery spasm may also develop in patients with angiographically normal coronary arteries.

Coronary artery spasm classically consists of recurrent episodes of rest pain with associated ST-segment elevation, which reverses with administration of nitrates (Prinzmetal angina). However, many patients present with atypical chest pain without ECG changes. Coronary angiography with acetylcholine provocation is used to diagnose coronary artery spasm, but the sensitivity and specificity are not known. Coronary artery spasm is treated with long-acting nitrates or calcium channel blockers.

Acute Coronary Syndromes

Acute coronary syndromes (ACSs) include unstable angina and acute MI (both ST-segment elevation and non–ST-segment elevation [NSTE] MI).

The resting ECG is essential for the evaluation and triage of a patient presenting with an ACS. Those without ST-segment elevation have unstable angina or NSTE MI (NSTE acute coronary syndrome [NSTE-ACS]), usually the result of subtotal coronary artery occlusion. Patients with ST-segment elevation generally have complete coronary artery occlusion leading to transmural injury.

Patients presenting with a suspected ACS require prompt evaluation. Those with ST-segment elevation must be treated on an emergency basis. Patients without ST-segment elevation can be evaluated in the chest pain unit of an emergency department; this approach allows discharge of low-risk patients, observation of intermediate-risk patients, and admission of high-risk patients (Figures 8.3 and 8.4).

[*]The baseline characteristics analyzed for Thrombolysis in Myocardial Infarction (TIMI) risk score for unstable angina and NSTE MI are the following:

- Age ≥65 years
- ≥3 CAD risk factors
- Known CAD (stenosis ≥50%)
- Aspirin use in past 7 days
- Increase in cardiac markers
- ST deviation ≥0.5 mm

Unstable Angina and NSTE-ACS

Pathophysiologic Factors

Unstable angina and NSTE-ACS are due to mismatched myocardial oxygen demand and supply, most often precipitated by conditions of decreased myocardial oxygen supply and usually due to coronary stenosis from nonocclusive thrombus at the site of a disrupted atherosclerotic plaque. Episodes may also be caused by increased myocardial oxygen demand in the presence of a fixed myocardial oxygen supply. Coronary spasm may precipitate episodes. Nocturnal ischemic symptoms are generally due to unstable angina and may be due to altered coronary tone or increased wall tension in patients with left ventricular dysfunction.

Biomarkers

Cardiac biomarkers are used to differentiate unstable angina from NSTE MI. Cardiac-specific troponins T and I are the preferred biomarkers. MI is defined by increased troponin T and I levels in the presence of symptoms of ischemia, and biomarker increases identify patients at high risk for future events.

Management

All patients with a possible ACS should have continuous ECG monitoring and treatment to improve the myocardial oxygen demand-supply mismatch. Sedation may decrease anxiety and catecholaminergic stimulation of the heart. β-Blockade is the treatment of choice to decrease myocardial oxygen demand.

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[*] Data from Antman EM, Cohen M, Bernink PJLM, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non–ST elevation MI: a method for prognostication and therapeutic decision making. JAMA. 2000 Aug 16;284(7):835-42.

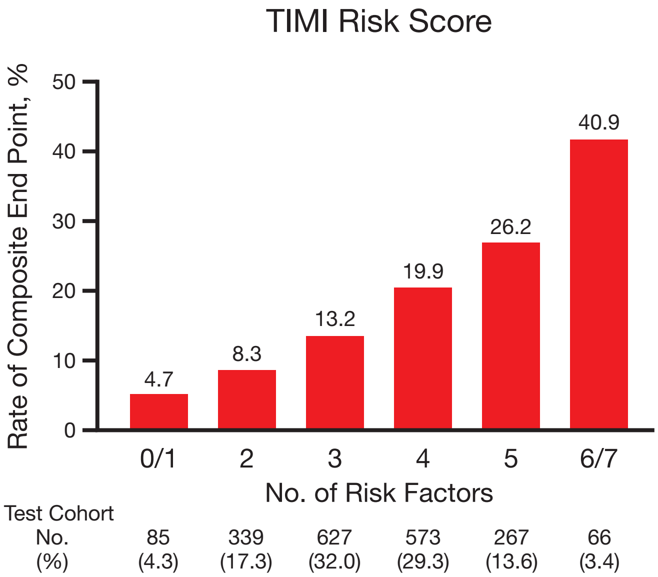

Figure 8.3. *The 14-Day Risk of Death, Myocardial Infarction, and Severe Ischemia Requiring Urgent Revascularization. Rates are based on number of risk factors present in the Thrombolysis in Myocardial Infarction (TIMI) trial cohort. "6/7" indicates 6 or 7.*

(From Antman EM, Cohen M, Bernink PJLM, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non–ST elevation MI: a method for prognostication and therapeutic decision making. JAMA. 2000 Aug 16;284[7]:835-42; used with permission.)

Antiplatelet agents, such as aspirin, are given immediately and decrease the incidence of progression to ST-segment elevation MI. Clopidogrel is an adenosine diphosphate-receptor antagonist that can be administered as an alternative for patients with aspirin allergy or intolerance. Other such antagonist agents include prasugrel and ticagrelor. Typically, dual antiplatelet support is provided during acute coronary syndrome and is a guideline-based recommendation. At the time of coronary angiography, however, findings such as triple-vessel disease or critical left main artery disease may suggest the benefit of CABG in such clinical settings. The administration of dual antiplatelet therapy before CABG predicts increased bleeding in the perioperative period; given this risk, if the patient is otherwise hemodynamically and electrically stable, surgery may be delayed up to 5 days to alleviate this increased perioperative bleeding risk. However, in clopidogrel-treated patients, urgent CABG may have an acceptable bleeding risk when performed by experienced surgeons.

Anticoagulation decreases the incidence of progression to MI and should be provided to all patients without contraindications. Continuous intravenous administration of unfractionated heparin or subcutaneous injections of low-molecular-weight heparin may be used. Bivalirudin (direct thrombin inhibitor) and fondaparinux (activated factor X inhibitor) are alternative anticoagulants. One important caveat is that fondaparinux is contraindicated at the time of percutaneous intervention because it has an increased risk of catheter-related thrombosis.

Conservative vs Invasive Strategy

There are 2 accepted therapeutic pathways for patients presenting with NSTE-ACS, depending on risk stratification. Patients at high risk should undergo an early invasive strategy (within 4-48 hours of admission) with revascularization (PCI or CABG) performed when appropriate. High-risk patients include those with a TIMI trial risk score of more than 3, ongoing chest pain, ST-segment depression on the resting ECG, and an increase in troponin levels. Use of clopidogrel or a glycoprotein IIb/IIIa inhibitor should be initiated before coronary angiography (Figure 8.5A and 8.5B).

A conservative (or selective invasive) strategy is indicated for non–high-risk patients and those who decline an invasive strategy. Initially, medical management is used for treatment. Coronary angiography is indicated if 1) recurrent ischemia occurs despite optimal medical therapy, 2) results of the predischarge stress test are positive, 3) left ventricular dysfunction (ejection fraction ≤40%) or heart failure is present, or 4) serious arrhythmias occur.

ST-Segment Elevation MI

Pathophysiologic Factors

An **ST-segment elevation MI** is the result of events occurring after rupture of an intracoronary plaque. Plaque rupture causes platelet adhesion and aggregation, thrombus formation, and sudden, complete occlusion of the artery. Without collateral circulation, 90% of the myocardium supplied by the occluded coronary artery is infarcted within 3 hours. Transmural MI develops if the

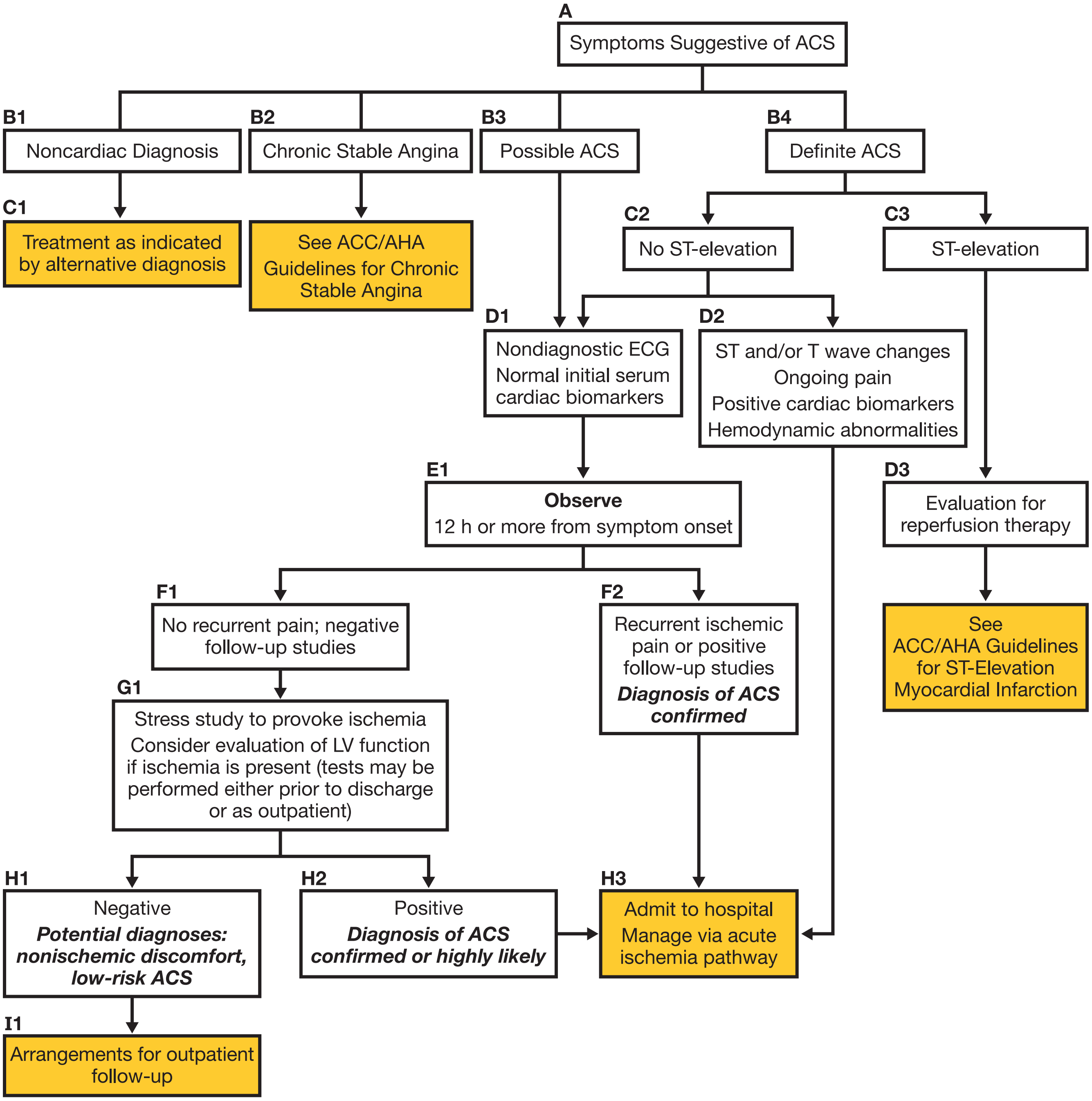
A
Symptoms Suggestive of ACS
B1
Noncardiac Diagnosis
B2
Chronic Stable Angina
B3
Possible ACS
B4
Definite ACS
C1
Treatment as indicated by alternative diagnosis
See ACC/AHA Guidelines for Chronic Stable Angina
C2
No ST-elevation
C3
ST-elevation
D1
Nondiagnostic ECG
Normal initial serum cardiac biomarkers
D2
ST and/or T wave changes
Ongoing pain
Positive cardiac biomarkers
Hemodynamic abnormalities
E1
Observe
12 h or more from symptom onset
D3
Evaluation for reperfusion therapy
F1
No recurrent pain; negative follow-up studies
F2
Recurrent ischemic pain or positive follow-up studies
Diagnosis of ACS confirmed
See ACC/AHA Guidelines for ST-Elevation Myocardial Infarction
G1
Stress study to provoke ischemia
Consider evaluation of LV function if ischemia is present (tests may be performed either prior to discharge or as outpatient)
H1
Negative
Potential diagnoses: nonischemic discomfort, low-risk ACS
H2
Positive
Diagnosis of ACS confirmed or highly likely
H3
Admit to hospital
Manage via acute ischemia pathway
I1
Arrangements for outpatient follow-up

Figure 8.4. *Algorithm for Evaluation and Treatment of Patients With Suspected ACS. ACC indicates American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; LV, left ventricular.*

(From Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, et al; American College of Cardiology; American Heart Association Task Force on Practice Guidelines [Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction]; American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons; American Association of Cardiovascular and Pulmonary Rehabilitation; Society for Academic Emergency Medicine. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction]: developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Circulation. 2007 Aug 14;116[7]:e148-304. Epub 2007 Aug 6. Erratum in: Circulation. 2008 Mar 4;117[9]:e180; used with permission.)

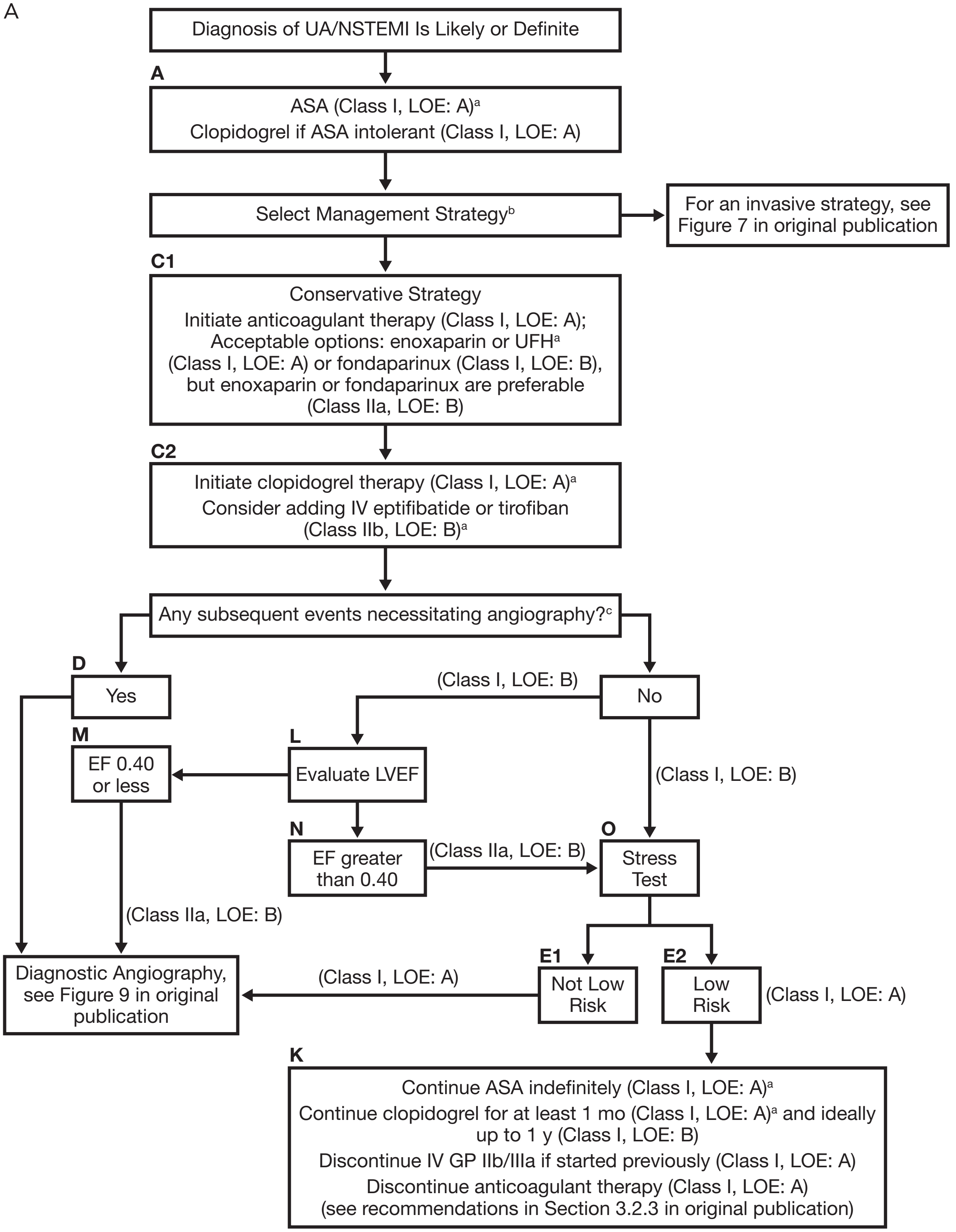
A
Diagnosis of UA/NSTEMI Is Likely or Definite
A
ASA (Class I, LOE: A)a
Clopidogrel if ASA intolerant (Class I, LOE: A)
Select Management Strategyb
For an invasive strategy, see Figure 7 in original publication
C1
Conservative Strategy
Initiate anticoagulant therapy (Class I, LOE: A);
Acceptable options: enoxaparin or UFHa
(Class I, LOE: A) or fondaparinux (Class I, LOE: B),
but enoxaparin or fondaparinux are preferable
(Class IIa, LOE: B)
C2
Initiate clopidogrel therapy (Class I, LOE: A)a
Consider adding IV eptifibatide or tirofiban
(Class IIb, LOE: B)a
Any subsequent events necessitating angiography?c
D
Yes
No
(Class I, LOE: B)
L
Evaluate LVEF
M
EF 0.40 or less
(Class I, LOE: B)
N
EF greater than 0.40
(Class IIa, LOE: B)
O
Stress Test
(Class IIa, LOE: B)
Diagnostic Angiography, see Figure 9 in original publication
(Class I, LOE: A)
E1
Not Low Risk
E2
Low Risk
(Class I, LOE: A)
K
Continue ASA indefinitely (Class I, LOE: A)a
Continue clopidogrel for at least 1 mo (Class I, LOE: A)a and ideally up to 1 y (Class I, LOE: B)
Discontinue IV GP IIb/IIIa if started previously (Class I, LOE: A)
Discontinue anticoagulant therapy (Class I, LOE: A)
(see recommendations in Section 3.2.3 in original publication)

Figure 8.5A. *Therapeutic Pathways for Patients With UA/NSTEMI Managed With an Initial Conservative Strategy.*

[a] See dosing in Table 13 of original publication. [b] See Table 11 of original publication for selection of management strategy. [c] Recurrent symptoms/ischemia, heart failure, or serious arrhythmia. Abbreviations are defined in the legend for Figure 8.5B.

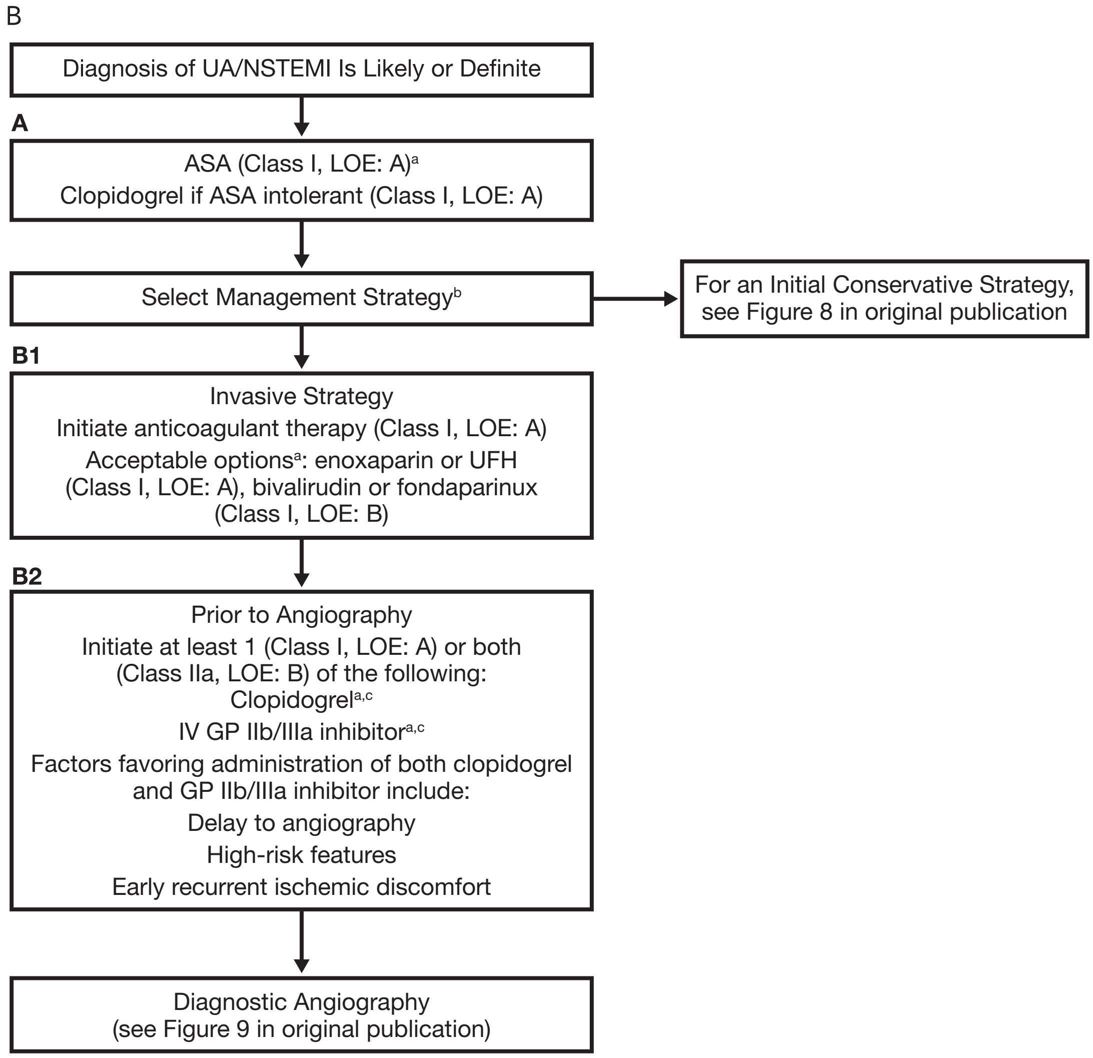
B
Diagnosis of UA/NSTEMI Is Likely or Definite
A
ASA (Class I, LOE: A)a
Clopidogrel if ASA intolerant (Class I, LOE: A)
Select Management Strategyb
For an Initial Conservative Strategy, see Figure 8 in original publication
B1
Invasive Strategy
Initiate anticoagulant therapy (Class I, LOE: A)
Acceptable optionsa: enoxaparin or UFH (Class I, LOE: A), bivalirudin or fondaparinux (Class I, LOE: B)
B2
Prior to Angiography
Initiate at least 1 (Class I, LOE: A) or both (Class IIa, LOE: B) of the following:
Clopidogrela,c
IV GP IIb/IIIa inhibitora,c
Factors favoring administration of both clopidogrel and GP IIb/IIIa inhibitor include:
Delay to angiography
High-risk features
Early recurrent ischemic discomfort
Diagnostic Angiography
(see Figure 9 in original publication)

Figure 8.5B. *Therapeutic Pathways for Patients With UA/NSTEMI Managed With an Initial Invasive Strategy.*

[a] See dosing in Table 13 of original publication. [b] See Table 11 of original publication for selection of management strategy. [c] Evidence exists that GP IIb/IIIa inhibitors may not be necessary if a patient received a preloading dose of at least 300 mg of clopidogrel at least 6 hours earlier (class I LOE B for clopidogrel administration) and bivalirudin is selected as the anticoagulant (class IIa, LOE B). ASA indicates acetylsalicylic acid; EF, ejection fraction; GP, glycoprotein; IV, intravenous; LOE, level of evidence; LVEF, left ventricular ejection fraction; UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction; UFH, unfractionated heparin. (Both A and B from Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction]. Circulation. 2007 Aug 14;116[7]:e148-e304. Epub 2007 Aug 6. Erratum in: Circulation. 2008 Mar 4;117[9]:e180; used with permission.)

condition is untreated. Patients with ST-segment elevation MI require urgent diagnosis and therapy to preserve the myocardium because prompt reperfusion therapy improves survival.

Key Definition

ST-segment elevation myocardial infarction: *the result of events occurring after rupture of an intracoronary plaque.*

MI is a major public health problem in the United States: About 1 million patients annually are admitted for an ACS, including MI. ST-segment elevation accounts for 20% of these cases. More than 30% of patients with MI die before reaching a hospital. With improved cardiac care, deaths from MI have decreased, primarily because of treatment of ventricular arrhythmias. β-Blockade has also decreased in-hospital and posthospital death rate by 30% to 40%. Reperfusion therapy has contributed to improved survival. Currently, the overall in-hospital mortality rate for patients with an ST-segment elevation MI is 5% to 10%.

Stunned myocardium occurs when reversible systolic dysfunction of the myocardium follows transient, nonlethal ischemia. With early reperfusion, contraction of the affected myocardium may be decreased and the myocardium continues to be viable. Myocardial stunning resolves hours to weeks after successful reperfusion.

The infarcted area may undergo thinning, dilatation, and dyskinesis. Myocardial remodeling may lead to congestive heart failure and increased mortality rate. Adverse infarct remodeling may be reduced with early initiation of neurohormonal therapies, including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (if angiotensin-converting enzyme inhibitors are contraindicated). β-Blockers can also help reduce long-term adverse infarct remodeling. However, they must be administered cautiously for the patient presenting with acute heart failure, in which further decompensation may be precipitated by the institution of β-blockade in the acute phase.

Presentation and Diagnosis

Patients with ST-segment elevation MI commonly present with anginalike pain lasting longer than 20 minutes and associated with typical ECG changes and increased levels of cardiac biomarkers (Figure 8.6). However, more than 25% to 30% of MIs are silent, and silent MIs often occur in patients with diabetes mellitus and in elderly patients. In addition, women having an MI often present without typical angina like pain. For women, symptoms such as nausea, jaw pain, upper back pain, and shortness of breath should be considered possible indicators of ischemia, in addition to chest pain or pressure.

An acute MI is usually diagnosed on the basis of ECG changes (ST elevation or depression or pathologic Q-wave development that meets criteria for diagnosis) in the setting of ischemic symptoms, biochemical markers of myocardial damage, or other evidence of myocardial damage not due to another potential cause.

KEY FACTS

- ✓ Acute coronary syndromes—include unstable angina and acute MI (both ST-segment elevation and NSTE MI)
- ✓ Cardiac biomarkers—used to differentiate unstable angina from n NSTE MI
- ✓ More than 25% of MIs are silent, and silent MIs often occur in patients with diabetes mellitus and in elderly patients
- ✓ Women having an MI often present without typical anginalike pain

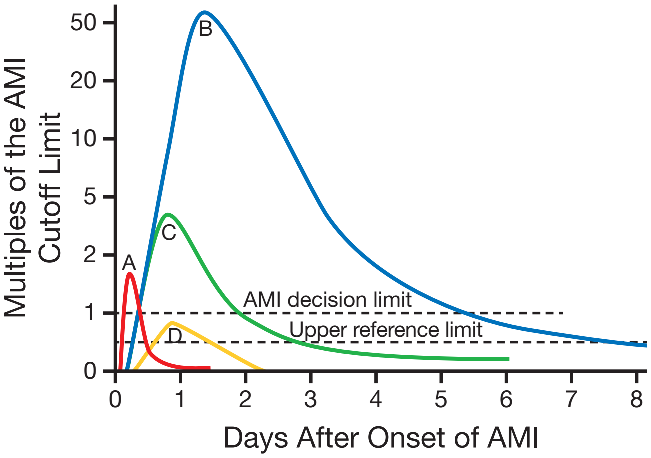

Figure 8.6. *Cardiac Biomarkers in Blood vs Time After Symptom Onset. Peak A, early release of myoglobin or CK-MB isoforms after AMI; peak B, cardiac troponin after AMI; peak C, CK-MB after AMI; peak D, cardiac troponin after unstable angina. Data are plotted on a relative scale, where 1.0 is set at the AMI cutoff concentration. AMI indicates acute myocardial infarction; CK-MB, MB isoenzyme of creatine kinase; STEMI, ST-segment elevation myocardial infarction.*

(From Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al; American College of Cardiology; American Heart Association Task Force on Practice Guidelines; Canadian Cardiovascular Society. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction]. Circulation. 2004 Aug 31;110[9]:e82-292. Errata in: Circulation. 2005 Apr 19;111[15]:2013-4. Circulation. 2007 Apr 17;115[15]:e411. Circulation. 2010 Jun 15;121[23]:e441; used with permission.)

Management

Bed rest, pain management, and sedation are essential and beneficial in the acute stage of MI to decrease myocardial oxygen demand. Oxygen administration has little benefit after 2 or 3 hours unless hypoxia (oxygen saturation <90%) is present. Modest hypoxemia is common as a result of ventilation-perfusion lung mismatch, even with uncomplicated MI. Continuous ECG monitoring is required to detect tachyarrhythmias and bradyarrhythmias.

Reperfusion therapy is the mainstay of management of ST-segment elevation MI. This is achieved chemically with fibrinolytic therapy or directly with percutaneous therapy. Both approaches require pharmacologic support with antiplatelet and anticoagulant medicines.

With regard to the antiplatelet therapy, a dual approach is invoked, including aspirin in addition to an adenosine diphosphate-receptor antagonist (clopidogrel, prasugrel, or ticagrelor). If fibrinolytic therapy is the reperfusion strategy that is used, then clopidogrel is the adenosine diphosphate-receptor antagonist of choice, simply because the other agents have not been adequately studied in this clinical setting. Aspirin (325 mg) reduces recurrent MI and death when given in addition to thrombolytic therapy and should be administered on admission. Clopidogrel (75 mg daily) is an alternative for patients with aspirin allergy or intolerance. After lytic therapy, clopidogrel therapy should be started on day 1 and continued during the hospitalization and for at least 1 month; ideally, it is continued for up to a year.

Glycoprotein IIb/IIIa inhibitors are given only if primary PCI is performed, and their use is generally initiated in the cardiac catheterization laboratory. They are not indicated for patients treated with thrombolytics because of the associated increase in bleeding risk. With the advent and widespread use of potent adenosine diphosphate-receptor antagonists, the role of glycoprotein IIb/IIIa antagonists is currently limited in contemporary practice. Typically, their role involves situations in which a large thrombus burden is found at the time of angiography or when inadequate loading has occurred with an adenosine diphosphate-receptor antagonist.

Anticoagulation prevents recurrent infarction (especially after thrombolytic therapy, which should be administered for at least 48 hours), deep vein thrombosis, and intracardiac thrombus formation. Long-duration anticoagulation is indicated for higher-risk patients (eg, large anterior MI for which reperfusion therapy was not given or was unsuccessful, atrial fibrillation, previous thromboembolic complication, presence of mechanical prosthetic valves). Thromboembolism is uncommon in patients in whom reperfusion therapy is successful. Unfractionated heparin or low-molecular-weight heparin can be used.

Nitroglycerin is useful for certain patients with MI—those with pulmonary edema, severely increased blood pressure, or persistent myocardial ischemia. Intravenous nitroglycerin should be given instead of long-acting oral nitrates. Nitrate intolerance develops with infusions of more than 24 hours in duration. Intravenous nitroglycerin should not be given for patients with low blood pressure (systolic <90 mm Hg) or right ventricular infarction or patients who have used a phosphodiesterase inhibitor (eg, sildenafil) within the previous 24 hours (48 hours for tadalafil).

β-Blockade during and after MI lowers mortality rate in the hospital and after discharge. Oral β-blockers should be administered at presentation to patients who do not have contraindications. Intravenous administration may be considered for hypertensive patients. Contraindications to β-blockers are bradycardia (heart rate <60 beats per minute), second- or third-degree atrioventricular block, hypotension (systolic blood pressure <100 mm Hg), acute heart failure, cardiogenic shock, and cocaine-induced MI. Beneficial effects include decreased pain, decreased myocardial oxygen demand, reduced ventricular fibrillation, decreased platelet aggregability, and decreased sympathetic effects on the myocardium. β-Blockers are most beneficial for patients with a large infarction who are at increased risk for complications.

Calcium channel blockers are generally not used for patients with an acute MI. However, diltiazem may be used to control ventricular rate in atrial fibrillation, especially if β-blockers are contraindicated and in the absence of serious left ventricular dysfunction. Amlodipine may be used to treat hypertension after the acute phase.

Angiotensin-converting enzyme inhibitors prevent ventricular remodeling, especially after a large anterior MI. Oral therapy may be initiated within the first 24 hours if blood pressure and renal function are stable. Angiotensin-converting enzyme inhibitors are indicated for patients with anterior infarction, congestive heart failure, diabetes mellitus, or a left ventricular ejection fraction less than 40%. It is reasonable to treat all patients after ST-segment elevation MI in the absence of hypotension or contraindications. Angiotensin receptor blockers are recommended as an alternative for patients who are intolerant of or allergic to angiotensin-converting enzyme inhibitors.

Long-term aldosterone blockade (spironolactone or eplerenone) is indicated for patients without renal dysfunction (creatinine, <2.0 mg/dL for women and <2.5 mg/dL for men) or hyperkalemia (potassium, <5.0 mEq/L) who are receiving therapeutic doses of angiotensin-converting enzyme inhibitors and β-blockers and have a left ventricular ejection fraction of less than 40% with either symptomatic heart failure or diabetes mellitus.

Magnesium does not seem to have a therapeutic role after MI and should be given only for the treatment of torsades de pointes or if a patient has documented hypomagnesemia of potential clinical significance.

Reperfusion Therapy

Early reperfusion therapy decreases risk of death by approximately 25%. The extent of myocardial salvage and degree of beneficial effect on mortality rate are measurably improved the earlier reperfusion occurs. Mortality rate is as low as 1% when fibrinolysis is given less than 90 minutes after the onset of pain. Most delays to reperfusion occur in the time to patient presentation, transport, and in-hospital institution of therapy. Reperfusion at 2 to 6 hours results in a lesser effect on myocardial salvage but still has an important effect on survival. Reperfusion therapy with fibrinolytics (thrombolytics) or primary PCI is indicated for patients presenting within 12 hours of onset of symptoms with the following findings: more than 1 mm of ST-segment elevation in 2 adjacent leads, a new (or presumably new) left bundle branch block, or a true posterior MI.

PCI is more effective than fibrinolysis for restoring normal coronary blood flow (TIMI grade 3) (90% vs 65%-70%). However, intravenous fibrinolysis allows faster administration and is more widely available. The preferred strategy depends on time since the onset of symptoms, transportation time to a skilled PCI laboratory, risk profile of the patient, and contraindications to fibrinolytics. Primary PCI is indicated for patients with immediate access to a high-volume catheterization laboratory, a contraindication to intravenous fibrinolysis, high-risk ST-segment elevation MI (eg, cardiogenic shock, pulmonary edema), or continued ischemia after thrombolytic therapy (ie, rescue PCI).

Routine immediate PCI after successful fibrinolytic therapy is not indicated in the absence of ongoing symptoms or ischemia. Reperfusion therapy with fibrinolysis is not indicated for patients with ST-segment depression or those who present late (>12 hours after symptom onset) and are asymptomatic without hemodynamic compromise or serious arrhythmia. Fibrinolytic therapy is less beneficial for patients age 75 years or older.

Major complications of intravenous fibrinolysis include major bleeding (5%-6%), intracranial bleeding (0.5%), and major allergic reaction (0.1%-1.7%). The incidence of myocardial rupture may be higher in patients who are given thrombolytic therapy late (>12 hours after pain onset). Several agents are available for intravenous fibrinolysis, including streptokinase (a nonselective thrombolytic agent) and tissue plasminogen activator (selectively binds to and lyses preformed fibrin). Tissue plasminogen activator has the fastest onset of action. The dose is 100 mg over 90 minutes. Thrombolytic agents such as reteplase and tenecteplase offer better selectivity for active thrombus, but their efficacy is equivalent to that of tissue plasminogen activator in clinical trials. Their greatest advantage is the ability to administer them as a bolus, which reduces drug errors and speeds delivery. Streptokinase is rarely used in the United States, and tenecteplase and reteplase are now the most commonly used fibrinolytics.

After administration of an intravenous fibrinolytic agent, a high-grade residual lesion is usually present. Reocclusion or ischemia occurs in 15% to 20% of patients and reinfarction occurs in 2% to 3%. Heparin should be given in conjunction with intravenous fibrinolysis, with tissue-specific plasminogen activators used to prevent reinfarction. The indications for coronary angiography or PCI after intravenous fibrinolysis are spontaneous or inducible ischemia, cardiogenic shock, pulmonary edema, ejection fraction less than 40%, and serious arrhythmias. Routine angiography after fibrinolysis is indicated, typically within 24 hours but after 2 to 4 hours of lytic drug administration in a strategy referred to as the *pharmacoinvasive approach*.

Acute Mechanical Complications of ST-Segment Elevation MI

Mechanical complications are relatively uncommon in patients who receive prompt reperfusion therapy. Mechanical complications include cardiogenic shock, myocardial free wall rupture, papillary muscle rupture, and ventricular septal defects. Right ventricular infarct may also occur after an inferior MI.

Most cases of cardiogenic shock are due to extensive left ventricular dysfunction. Echocardiography is helpful to determine the mechanism of cardiogenic shock. The mortality rate from cardiogenic shock is 50% (Table 8.3).

Right ventricular infarction occurs in up to 40% of patients with inferior MI and typically involves occlusion of the proximal right coronary artery. It can present hours to days after the initial infarction and is diagnosed from increased jugular venous pressure in the presence of clear lung fields. ST-segment elevation in lead V_4R is diagnostic of a large right ventricular infarction and portends increased mortality risk. In extreme circumstances, right ventricular infarction can cause cardiogenic shock due to compromised filling of the left ventricle. Treatment includes intravenous fluid resuscitation; if this is inadequate, consideration of the addition of an inotropic agent may be reasonable. In the clinical setting of a right ventricular infarction, dobutamine is the inotropic agent of choice. When right ventricular infarction is recognized early, reperfusion therapy is indicated. After the acute complication is treated and the patient is supported through the illness, recovery is usually the rule.

Myocardial free wall rupture causes abrupt decompensation. It usually occurs 2 to 14 days after transmural MI, occurs most commonly in elderly hypertensive women, and usually presents as electromechanical dissociation or death. Tamponade may occur if the rupture is contained in the pericardium. If the diagnosis can be made with emergency echocardiography, surgical treatment should be performed. If the rupture is sealed off,

Table 8.3 • Diagnosis of Cause of Cardiogenic Shock

	Test Results				
	Pulmonary Artery Catheterization[a]				
Cause	**RAP**	**PAWP**	**CO**	**Catheterization**	**Two-Dimensional Echocardiography**
Left ventricular dysfunction	↑	↑↑	↓↓	NA	Poor strength of left ventricle
Right ventricular infarction	↑↑	↓	↓↓	NA	Dilated right ventricle
Tamponade	↑↑	↑↑	↓↓	End equalization	Pericardial tamponade
Papillary muscle rupture	↑↑	↑↑	↓↓	Large V	Severe mitral regurgitation
Ventricular septal defect	↑	↑↑	↑	Step-up	Defect seen
Papillary emboli	↑↑	=	↓	PADP>PAWP	Dilated right ventricle

Abbreviations: CO, cardiac output; NA, not applicable; PADP, pulmonary artery diastolic pressure; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure.

[a] ↑ indicates elevated; ↑↑, very elevated; ↓, decreased; ↓↓, very decreased.

a pseudoaneurysm may occur. Surgical treatment is required because of the unpredictable nature of pseudoaneurysms in the early stage of formation. Unfortunately, the mortality rate in this setting is extremely high.

Papillary muscle rupture usually occurs 2 to 10 days after an MI. It is associated with inferior MI because of the single blood supply to the posteromedial papillary muscle. Rupture of papillary muscle is heralded by the sudden onset of dyspnea and hypotension. Although a murmur may be present, it may not be audible because of equalization of left atrial and left ventricular pressures. An intra-aortic balloon pump can be used to temporarily stabilize the patient's condition, and emergency operation is done for definitive therapy.

Ventricular septal defects usually occur 1 to 20 days after MI and are equally frequent in inferior and anterior MIs. Ventricular septal defects associated with inferior MIs have a poorer prognosis because of the serpiginous nature of the rupture and associated ventricular infarction. They are indicated by the abrupt onset of dyspnea and hypotension. A loud murmur and systolic thrill are almost always present. The diagnosis is made with echocardiography. Hemodynamic status may be temporarily stabilized with use of an intra-aortic balloon pump while awaiting definitive surgical management.

Evaluation Before Hospital Discharge

Risk stratification for long-term outcomes is required before hospital discharge and typically includes left ventricular function determination, assessment of risk of arrhythmias, and identification of inducible ischemia. A submaximal treadmill test can be performed before discharge, at 4 to 6 days after MI. Alternatively, a symptom-limited treadmill test can be performed safely 10 to 21 days after MI. If a submaximal treadmill test is performed before discharge, a late symptom-limited treadmill test should be performed at follow-up evaluation 3 to 6 weeks after MI. High-risk patients identified by treadmill exertion testing have an ST-segment depression more than 1 mm, a decrease in blood pressure, or an inability to achieve 4 metabolic equivalents on the exercise test. Imaging exercise tests may identify additional high-risk patients by demonstrating multiple ischemic areas. Pharmacologic stress tests (dobutamine echocardiography, dipyridamole thallium scanning, or adenosine thallium scanning) may be useful for patients unable to exercise.

Increasingly, rather than a stress test, a delayed invasive (pharmacoinvasive) strategy is being practiced in which coronary angiography is performed at least 4 hours after fibrinolysis and before hospital discharge in the setting of ST-segment elevation MI. PCI is performed in the majority of patients, and few patients undergo CABG or medical therapy alone. The choice between PCI and CABG is based on factors similar to those used to make the decision for patients with stable coronary artery disease. This strategy is associated with lower rates of recurrent ischemia and infarction compared with the ischemia-guided approach described above.

Optimal risk factor modification is essential, including an exercise program, weight loss, and dietary modifications. The goal of treatment is to decrease the LDL-C level to 100 mg/dL or less (optimal, <70 mg/dL). If the level is more than 100 mg/dL, statin treatment should be initiated before discharge. All tobacco users should be counseled and nicotine cessation must be stressed.

Aspirin and statins decrease recurrent MI and death and should be given to all patients unless contraindicated. β-Blockers improve survival after MI and are most effective in high-risk patients (ie, patients with decreased left ventricular function and ventricular arrhythmias). Long-term therapy may not be required for low-risk patients. Antiarrhythmic agents are associated with increased mortality rate and should not be used to suppress ventricular ectopy. Angiotensin-converting enzyme inhibitors decrease the mortality rate after anterior MI and depressed left ventricular function, presumably by inhibiting infarct remodeling. A rehabilitation program is essential for the patient's well-being and cardiovascular fitness. An automatic implantable cardioverter-defibrillator should be considered if the ejection fraction is less than 35% at 40 days after MI of patients with an expected survival of at least 1 year.

KEY FACTS

- ✓ Early reperfusion therapy for ST-segment elevation MI—decreases mortality rate by approximately 25%
- ✓ Routine angiography after fibrinolysis for ST-segment elevation MI—is indicated, typically within 24 hours but after 2-4 hours of lytic administration in a strategy referred to as *the pharmacoinvasive approach*
- ✓ Risk stratification for long-term outcomes after ST-segment elevation MI—required before hospital discharge and typically includes left ventricular function determination, assessment of risk of arrhythmias, and identification of inducible ischemia
- ✓ Automatic implantable cardioverter-defibrillator—should be considered when the ejection fraction is <35% at 40 days after MI in patients with an expected survival of ≥1 year

9

Pericardial Disease and Cardiac Tumors

KYLE W. KLARICH, MD

Pericardial Disease

The pericardium consists of a fibrous sac and a serous membrane. The space between visceral and parietal pericardium normally contains 15 to 25 mL of clear fluid. The pericardium functions to prevent cardiac distention, limit cardiac displacement (by its attachment to neighboring structures), and protect the heart from inflammation.

Acute or Subacute Inflammatory Pericarditis

Symptoms

The chest pain of pericarditis is aggravated by inspiration, coughing, and movement of the trunk. The pain can be relieved by sitting up. Usually but not exclusively described as *sharp* and *stabbing*, it may radiate to the shoulder, neck, arms, and back. A low-grade fever and malaise may occur.

Diagnosis

On physical examination, a 3-component pericardial friction rub is considered diagnostic when heard, but it is variably present. Typically, the murmur may change with positional changes, and therefore patients should be auscultated in several positions—sitting, leaning forward, supine, and left and right decubitus. Chest radiography is usually normal, but globular enlargement may be found if the effusion is marked (>250 mL). A pulmonary infiltrate or small pleural effusion may be present. Left pleural effusion predominates for unknown reasons. Blood work specifically for increases in white cell count, sedimentation rate, and high-sensitivity C-reactive protein level can lend supportive evidence of inflammation. Troponins may be increased if the patient has myopericarditis.

Electrocardiography (ECG) shows acute, concave ST elevation in all ventricular leads. The PR segment is depressed in the early stages and can be helpful in distinguishing pericarditis from myocardial injury. T-wave inversion is rare to see with pericarditis, and the ST changes are usually diffuse and outside of typical coronary distribution. Q waves are generally absent. Echocardiography is helpful in the determination of hemodynamic significance and whether there is an associated effusion, but it is not diagnostic and may be relatively benign. Cardiac computed tomography (CT) or magnetic resonance imaging (MRI) can be helpful to determine an increased pericardial thickness and, with cardiac MRI, to determine inflammation through use of delayed gadolinium enhancement. Ultimately, pericarditis is a clinical diagnosis that requires at least 2 of the following 4 components: characteristic pleuritic chest pain, pericardial friction rub, typical electrocardiographic changes, and a new or worsening pericardial effusion.

Causes

Causes include viral or idiopathic pericarditis, which is the most common cause in the community presentation. With idiopathic and viral causes, pericarditis incidence decreases with age.

The differential diagnosis of pericarditis includes 1) idiopathic cause, 2) infection (bacterial; may include tuberculosis and viral), 3) postmyocardial infarction, 4) uremia, 5) chest trauma, 6) underlying systemic condition (eg, collagen vascular disease), 7) procedural complication (catheter ablation, device placement, or cardiac surgery), 8) radiotherapy (acute and delayed presentation), and 9) neoplasm (eg, Hodgkin lymphoma, leukemia, breast cancer).

Management of idiopathic and presumed viral pericarditis is with anti-inflammatory agents and typically follows a benign course, with relapses occurring in 10% to 30% of cases. With other causes of pericardial pain, an anti-inflammatory treatment may be helpful for symptom management, but here, treatment of the underlying cause should be the focus. Ibuprofen is preferred because of its lower incidence of adverse effects, wide dose range, and favorable effects on coronary blood flow. The typical dose is 300 to 800 mg every 6 to 8 hours. Aspirin (2-4 g daily in divided doses) is preferred for patients with pericarditis associated with myocardial infarction. Indomethacin may reduce coronary blood flow and should be used with caution for patients with coronary artery disease. Colchicine also is used to help with acute symptoms and prevent recurrence.

NSAIDs should be given in a high dose with gastrointestinal tract protection for 1 to 2 weeks, followed by a slow taper over 4 to 6 weeks. Colchicine is given for a prolonged course: 1 to 2 mg the first day, followed by 0.6 mg once daily for 3 to 6 months. Systemic corticosteroids should not be used as first-line therapy for idiopathic or viral pericarditis because they have been associated with increased rates of recurrent pericarditis.

Pericardial Effusion

The pericardium exudes fluid, fibrin, and blood cells in response to inflammation, causing a pericardial effusion. It cannot be seen on chest radiography until the effusion is 250 mL. With slow fluid accumulation, the pericardial sac distends slowly with no cardiac compression. With rapid accumulation (eg, bleeding), tamponade can occur with relatively small amounts of fluid. Tamponade restricts ventricular filling, decreasing ventricular volume. Increased intrapericardial pressure increases ventricular end-diastolic pressure, and increased mean atrial pressure increases the venous pressure. Decreased ventricular volume and filling diminish cardiac output. Any cause of pericarditis can cause tamponade, but acute causes of hemopericardium should be considered (eg, ruptured myocardium after infarction, aortic dissection, ruptured aortic aneurysm, sequelae of cardiac operation).

Clinical Features

Tamponade produces a continuum of characteristics, depending on its severity. Typical findings are low blood pressure, a small and quiet heart, tachycardia, increased jugular venous pressure (JVP), and pulsus paradoxus (enhanced systemic blood pressure drop during inspiration due to decreased left ventricular filling). Kussmaul sign (increased distention of the neck veins during inspiration) also may occur with constrictive pericarditis. ECG may show low voltage owing to the fluid accumulation and tachycardia due to low stroke volume and hemodynamic compromise.

Diagnosis

Echocardiography is diagnostic of pericardial tamponade and can inform the cause and guide therapy.

Treatment

Supportive measures of fluid ressessation are helpful transiently. Usually, echocardiography-guided emergency pericardiocentesis is necessary for hemodynamically compromised patients.

Constrictive Pericarditis

Constrictive pericarditis is caused by a scarred pericardium. Observed clinical symptoms and hemodynamics are due to an inelastic pericardium that typically is thickened and fibrotic but in some cases may be inflamed. The clinical presentation is characterized by dissociation of respiratory-induced changes in intrathoracic and intracardiac pressures. Ventricular filling is limited by the constraining pericardium, an effect leading to lower ventricular volume, higher end-diastolic pressure, and decreased cardiac output. The most common causes are recurrent viral pericarditis, irradiation, previous open heart operation, tuberculosis, and neoplastic disease.

Symptoms

Symptoms of constrictive pericarditis are predominantly right-sided heart failure, peripheral edema, ascites, and often dyspnea and fatigue.

Physical Examination

In constrictive pericarditis, JVP is increased (best observed when the patient is sitting or standing) and neck veins are distended on inspiration (Kussmaul sign). The JVP may show rapid descents; a pericardial knock is present in less than one-half of the cases. Ascites and peripheral edema are usually present. Chest radiography may show pericardial calcification and cardiac enlargement. No specific changes are found on ECG.

Diagnosis

A high degree of clinical suspicion is necessary because the diagnosis of constrictive pericarditis can be challenging. Echocardiography, particularly with Doppler, shows the hemodynamic effects of respiratory changes in mitral and tricuspid inflow velocities and other classic changes. Pericardial thickness may be delineated by CT and MRI, but up to 20% of constraining pericardium may not be thickened according to CT criteria. Magnetic resonance scanning can show pericardial thickness, respiratory variation, and inflammation that, if present, can inform the nature of therapy. Restrictive cardiomyopathy is the main differential diagnosis, and differentiation can be difficult. Myocardial disease is likely if pulmonary artery systolic pressure is more than 50 mm Hg or if end-diastolic pulmonary artery pressure is more than 30% of systolic pressure, but both are nonspecific findings. In difficult cases, cardiac catheterization for hemodynamic measurements may be necessary to show the intraventricular dependence and dissociation of intracardiac and intrathoracic pressures. Constrictive pericarditis is a reversible cause of heart failure and should be considered in all patients presenting with symptoms of predominantly right heart failure.

Treatment

Pericardiectomy is the treatment of choice for chronic, constrictive pericarditis without evidence of ongoing inflammation. However, a growing body of literature is emphasizing use of cardiac magnetic resonance scanning to assess for inflammation and if present, consideration of anti-inflammatory therapy may be entertained initially.

KEY FACTS

- ✓ Acute or subacute inflammatory pericarditis—pericardial friction rub may be variable, chest radiography is usually normal, but globular enlargement may be found if effusion is marked (>250 mL)
- ✓ Acute or subacute inflammatory pericarditis—idiopathic viral pericarditis is the most likely diagnosis in the absence of a definable cause, and treatment with high-dose aspirin or other NSAIDs and colchicine usually resolves the condition
- ✓ Pericardial effusion—any cause of pericarditis can cause tamponade, but acute causes of hemopericardium should be considered (eg, ruptured myocardium after infarction, aortic dissection, ruptured aortic aneurysm, and sequelae of cardiac operation)
- ✓ Constrictive pericarditis—includes the following characteristics:
    - The JVP is increased (best observed when the patient is sitting or standing) and neck veins are distended on inspiration (Kussmaul sign)
    - A high degree of clinical suspicion is necessary because the diagnosis can be challenging
    - This reversible cause of heart failure should be considered in all patients presenting with symptoms of predominantly right heart failure

Cardiac Tumors

Metastatic tumors are far more common than primary cardiac tumors (>40-fold). The most frequent metastases to the heart are melanoma, lymphoma, and breast, lung, and esophageal tumors. Patients with metastatic malignancies have metastatic disease to the heart up to 15% of the time. More than one-half of patients with malignant melanoma have metastases to the heart. Metastatic disease to the heart carries a poor prognosis.

Primary tumors of the heart are rare. The most common primary tumors of the adult heart are benign and include cardiac myxoma, papillary fibroelastoma, lipoma, and fibroma, in order of frequency. Cardiac tumors may cause circulatory problems, valve dysfunction, myocardial infiltration–related complications, invasion into local structures, or embolization.

The most common primary cardiac tumors are papillary fibroelastoma (PFE) and myxoma. These are benign tumors with not-so-benign consequences of stroke and systemic embolization in the case of both entities.

Most cardiac myxomas are sporadic, but a subset of these tumors are familial. Most (75%-85%) are located in the left atrium, 18% are in the right atrium, and the rest are ventricular. Most atrial tumors arise from the atrial septum, usually adjacent to the fossa ovalis. About 95% are solitary. Most have a short stalk, are gelatinous and friable, and tend to embolize. They occasionally calcify and may be visible on chest radiography. **Carney complex**, a familial syndrome, involves multiple, often recurrent, cardiac and extracardiac myxomas, lentiginosis (spotty pigmentation) and other blue nevi, endocrine tumors, and schwannomas. Myxomas present at a young age compared with sporadic myxomas.

Key Definition

Carney complex: *a familial myxoma syndrome that involves multiple endocrine neoplasias and multiple myxomas.*

Blood flow obstruction, embolization, and systemic effects are the most common complications. Systemic emboli may occur in 30% to 60% of patients with left-sided myxoma, frequently to the brain and lower extremities. Coronary embolization is rare, but it should be considered in a young patient with no known previous cardiac disease. Systemic effects are fatigue, fever, weight loss, and arthralgia. The systemic effects may be associated with an increased sedimentation rate, leukocytosis, hypergammaglobulinemia, and anemia. Increased immunoglobulins are usually of the immunoglobulin G class.

Left atrial tumors prolapse into the mitral valve orifice, producing symptoms of mitral stenosis (dyspnea, orthopnea, cough, pulmonary edema, and hemoptysis) and can even lead to syncope or sudden cardiac death. Classically, symptoms occur with a change in body position. Physical findings suggest mitral stenosis. Pulmonary hypertension may occur. An early diastolic sound, a tumor "plop," may be heard with the timing of a third heart sound. The later timing and lower frequency differentiate it from an opening snap.

Echocardiography allows accurate diagnosis, augmented by cardiac MRI, which can differentiate tumor from thrombus. After diagnosis, myxomas should be excised surgically.

PFEs are seen incidentally or in the workup for a source of embolization. They are not usually associated with any valvular dysfunction. Echocardiography allows accurate diagnosis, where they are seen as small (usually <1 cm), highly mobile masses, a stalk, and a head. These neoplasms have been reported on every endocardial surface but have a propensity for valve tissue. The differential diagnosis includes vegetation due to bacterial endocarditis and nonbacterial thrombotic endocarditis (in the clinical setting of lupus, antiphospholipid syndrome, or malignancy). They have been associated with systemic embolization, and when patients are candidates for cardiac surgery, this therapy could be considered in a center of excellence with experience in PFE removal, where a greater-than-95% chance of valve preservation is possible.

KEY FACTS

- ✓ Cardiac tumors—metastatic tumors are far more common than primary cardiac tumors (>40-fold)
- ✓ The most common primary benign tumors of adult heart—cardiac myxoma, papillary fibroelastoma, lipoma, and fibroma
- ✓ Left atrial tumors—prolapse into the mitral valve orifice, producing symptoms of mitral stenosis (dyspnea, orthopnea, cough, pulmonary edema, and hemoptysis) and can even lead to syncope or sudden cardiac death

10 Valvular and Congenital Heart Diseases[a]

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Valvular Heart Disease

Aortic Stenosis

The pathophysiologic effect of aortic stenosis on the heart is pressure overload, leading to left ventricular (LV) hypertrophy. Most cases of aortic stenosis are due to valvular stenosis.

Types

The *congenital bicuspid* type of aortic stenosis occurs in 2% of the population; the male to female ratio is 3:1. It is inherited in an autosomal dominant pattern. First-degree relatives should be screened for bicuspid valve and ascending aortic aneurysm. Bicuspid aortic valve (BAV) is the most common cause of aortic stenosis in adults younger than 55 years. It is often associated with ascending aortic dilatation and dissection, occurring at a younger age than in patients with idiopathic aortic aneurysms. BAV disease carries a 6% lifetime risk of aortic dissection, 9 times higher than that of the general population with aortic valve. Ascending aortic complications occur in approximately 35% of persons with BAV, many of whom require surgical management (Circulation. 2005 Feb 22;111[7]:832-4; Heart Lung Circ. 2008 Oct; 17[5]:357-63; Heart. 2000 Jan;83[1]:81-5) and routine follow-up. Biner et al (J Am Coll Cardiol. 2009 Jun 16;53[24]:2288-95) documented that aortic root dilation is relatively prevalent (32%) in first-degree relatives of BAV patients. Aortic root dilation also was present in relatives with 3-leaflet aortic valve morphologic characteristics. BAV may be associated with coarctation of the aorta in about 5% of patients. Conversely, if coarctation is noted, the patient has a 30% to 50% chance of BAV. Frequently, when a patient is young and the valve is still pliable, the auscultation is different from degenerative aortic valve disease.

An ejection click classically precedes the systolic murmur and may be heard even in the absence of murmur or before the murmur is present. This is a high-pitched sound that comes early in systole, right after the first heart sound. The ejection click represents the opening of the less pliable bicuspid valve and is a high-pitched sound heard best in the aortic listening post, the second intercostal space, and with the diaphragm of the stethoscope. As aortic stenosis worsens, the aortic valve closure is delayed; when aortic stenosis is severe, there may even be paradoxic splitting of the second heart sound.

If BAV is suspected, the diagnosis usually can be made with transthoracic echocardiography. If transthoracic echocardiographic images are nondiagnostic, transesophageal echocardiography or cardiac computed tomography (CT) can be used to define the aortic valve anatomy. If the diagnosis is confirmed, the aorta should be imaged with ultrasonography, magnetic resonance imaging, or CT to rule out coarctation and aortic dilatation or aneurysm.

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[a] Portions previously published in Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, et al; 2006 Writing Committee Members; American College of Cardiology/American Heart Association Task Force. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2008 Oct 7;118(15):e523-661. Epub 2008 Sep 26; used with permission.

Degenerative aortic valve disease due to calcification is the most common cause of aortic stenosis in adults older than 55 years. The valve is tricuspid. When calcification is extensive, the aortic valve component becomes inaudible.

The *rheumatic* type of aortic valve disease is less common. It is associated with thickening and fusion of the aortic cusps at the commissures. It always occurs with a rheumatic mitral valve, although considerable mitral stenosis or regurgitation is not always evident. It usually occurs in adulthood (age 40-60 years), usually 15 plus or minus 5 years after acute rheumatic fever.

Symptoms

The classic symptoms of the valvular type of aortic stenosis (regardless of type) include exertional dyspnea, syncope, angina, and sudden cardiac death. The onset of symptoms is an ominous sign and portends a poor prognosis. Patients with symptomatic aortic stenosis need rapid surgical intervention; there is no medical treatment. The presence of angina does not necessarily indicate coexisting coronary disease, but it can be secondary to increased LV oxygen supply-demand mismatch.

Physical Examination

The arterial pulse is parvus (small and difficult to feel) and tardus (delayed) in hemodynamically significant aortic stenosis. The LV impulse is localized, lateralized, and sustained. Arterial thrills may be palpable at the carotid artery, suprasternal notch, second intercostal space, or left and right sternal borders. An audible and palpable fourth heart sound may be present. The aortic valve component is diminished and delayed and may even become absent with decreasing pliability of the aortic cusps. The ejection systolic murmur becomes louder and peaks later with increasing severity, radiating to the carotid arteries and the apex.

Diagnosis

Electrocardiography of aortic stenosis may show LV hypertrophy. By comparison, echocardiography is more sensitive and specific. Left bundle branch block is common; in later stages of the condition, conduction abnormalities may develop (eg, complete heart block) if calcium impinges on the conducting system. On chest radiography, the heart size is usually normal even when stenosis is severe and the left ventricle fails. Enlargement of the heart may not be evident until late stages and LV remodeling occurs. The aortic root may show *poststenotic* dilatation, now recognized as an aortopathy when the valvular abnormality is bicuspid. In degenerative aortic valve disease, calcium may be seen in the valve leaflets and the intervalvular fibrosa, especially on a lateral view.

The differential diagnosis of aortic stenosis has 2 components. They are hypertrophic cardiomyopathy (a different carotid upstroke and change in murmur with Valsalva maneuver) and mitral regurgitation (murmur may radiate anteriorly and upward along the aorta, particularly with rupture of the chordae of the posterior mitral valve leaflet; no radiation of murmur occurs to carotid arteries).

Aortic stenosis can be diagnosed with a bedside physical examination. The most important physical finding is the parvus and tardus pulse contour. The degree of aortic stenosis can be difficult to determine on the basis of physical examination alone. Noninvasive Doppler echocardiography is useful for assessing aortic valve area and gradients and correlates well with invasive catheter-based assessment of the same. Severe aortic stenosis is present when the mean Doppler gradient is more than 40 mm Hg, the valve area is less than 1.0 cm^2, and the valve index is 0.6 cm^2/m^2 or less. Progression of aortic stenosis is highly variable; on average, it is about 0.12 cm^2 per year. Progression to symptoms can be insidious; the onset of clinical symptoms is an ominous prognostic sign. Survival is limited after symptom onset, and intervention should be seriously considered because there is no medical management option.

Treatment

All patients should be educated about worrisome symptoms that may develop. Dyspnea, chest pain, angina, syncope, or newly diagnosed congestive heart failure are important clinical evidence for surgical intervention and should be promptly evaluated (Table 10.1). Aortic valve replacement is the only effective treatment for patients with severe obstruction (Figure 10.1). In recent years, a percutaneous option for aortic valve replacement is available for patients with intermediate surgical risk or greater. Evaluation of the ascending aorta offers an important decision point for patients with BAV. The aortic

Table 10.1 • Quantification of Severity of Aortic Stenosis and Treatment Guidelines

Severity	AVA, cm^2	AVA Index, cm^2/m^2	Gradient, mm Hg	Follow-up or Treatment
Normal	3.0-4.0		<10	None
Mild	>1.5	>0.8	<30	Echo every 5 years or if symptoms
Moderate	1.0-1.5	0.5-0.8	30-40	Monitor for symptoms Echo every 1-2 years
Severe	<1.0	<0.5	>40	Symptoms: operate No symptoms: echo every 6-12 months

Abbreviations: AVA, aortic valve area; echo, echocardiography.

Data from Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, et al; 2006 Writing Committee Members; American College of Cardiology/American Heart Association Task Force. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2008 Oct 7;118(15):e523-661. Epub 2008 Sep 26.

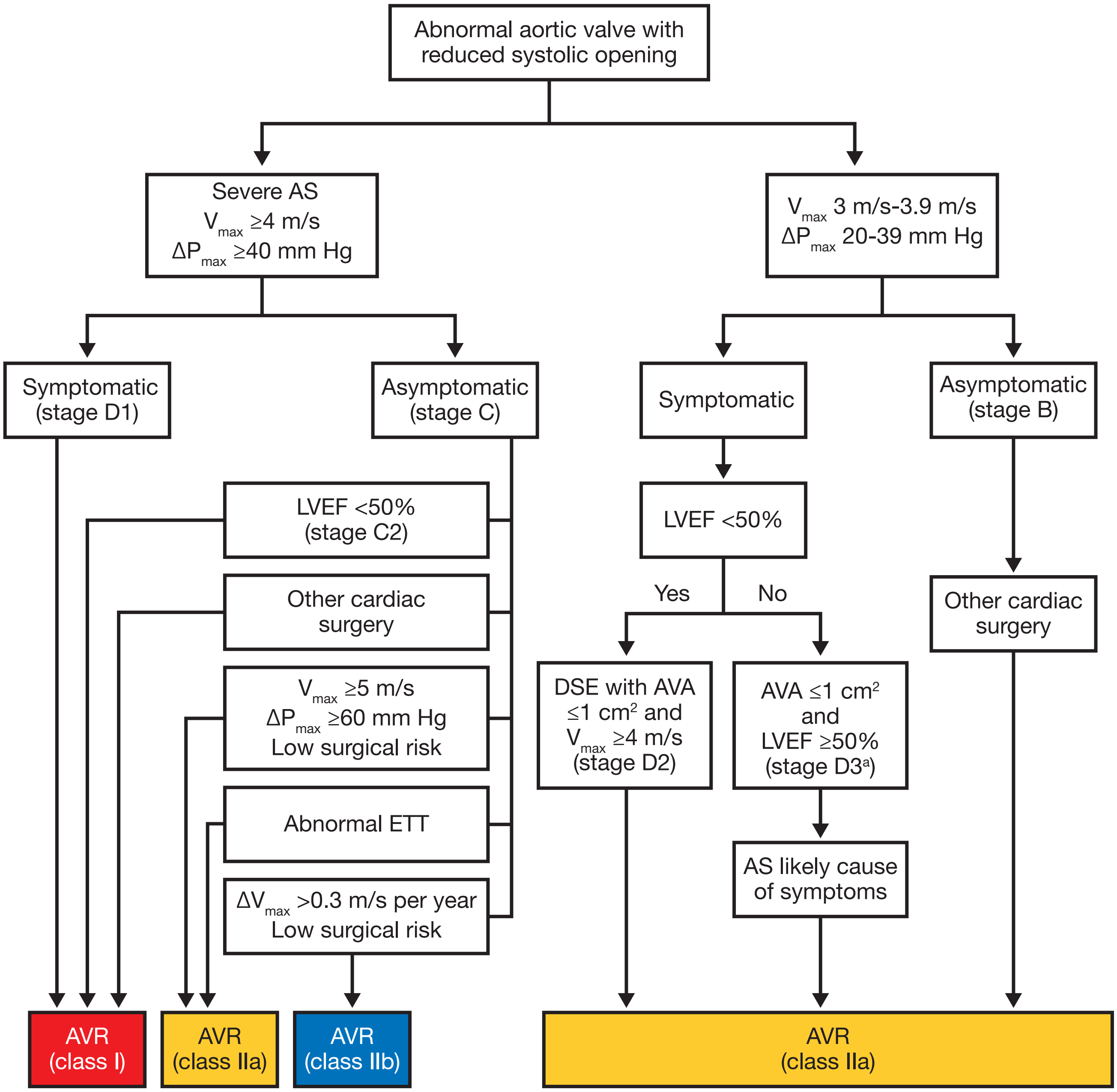

Abnormal aortic valve with reduced systolic opening
Severe AS
V_{max} ≥4 m/s
ΔP_{max} ≥40 mm Hg
V_{max} 3 m/s-3.9 m/s
ΔP_{max} 20-39 mm Hg
Symptomatic (stage D1)
Asymptomatic (stage C)
Symptomatic
Asymptomatic (stage B)
LVEF <50% (stage C2)
Other cardiac surgery
V_{max} ≥5 m/s
ΔP_{max} ≥60 mm Hg
Low surgical risk
Abnormal ETT
ΔV_{max} >0.3 m/s per year
Low surgical risk
LVEF <50%
Yes
No
DSE with AVA ≤1 cm² and V_{max} ≥4 m/s (stage D2)
AVA ≤1 cm² and LVEF ≥50% (stage D3ª)
AS likely cause of symptoms
Other cardiac surgery
AVR (class I)
AVR (class IIa)
AVR (class IIb)
AVR (class IIa)

Figure 10.1. *Indications for Aortic Valve Replacement (AVR), Surgical or Transcatheter Approach, in Patients With Aortic Stenosis (AS). Arrows show the decision pathways that result in a recommendation for AVR. Periodic monitoring is indicated for all patients in whom AVR is not yet indicated, including those with asymptomatic AS (stage D or C) and those with low-gradient AS (stage D2 or D3) who do not meet the criteria for intervention. AVA indicates aortic valve area; DSE, dobutamine stress echocardiography; ETT, exercise treadmill test; LVEF, left ventricular ejection fraction;* ΔP_{max}*, maximum pressure gradient;* V_{max}*, maximum velocity.* [a] *AVR should be considered with stage D3 AS only if valve obstruction is the most likely cause of symptoms, stroke volume index is less than 35 mL/m², indexed AVA is less than or equal to 0.6 cm²/m², and data are recorded when the patient is normotensive (systolic blood pressure <140 mm Hg).*

(From Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al; ACC/AHA Task Force Members. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 10;129[23]:e521-643. Epub 2014 Mar 3. Errata in: Circulation. 2014 Jun 10;129[23]:e651. Circulation. 2014 Sep 23;130[13]:e120. Dosage error in article text; used with permission.)

valve should be replaced at 5 cm if risk factors are present (ie, family history of dissection or increased rate of expansion [≥0.5 cm/year]). The patient may have an elective replacement at 5.5 cm if no risk factors exist and at 4.5 cm if simultaneous aortic valve surgery is indicated.

Aortic Regurgitation

The pathogenesis of aortic regurgitation is that of volume and pressure overload on the left ventricle, leading to hypertrophy and dilatation. It can be related to either the aortic valve or the aortic root and can be acute or chronic (Table 10.2). Acute aortic regurgitation may be associated with an aortic dissection.

Valvular Aortic Regurgitation

Valvular aortic regurgitation has several possible causes. They are 1) congenital BAV, 2) rheumatic fever, 3) endocarditis, 4) degenerative aortic valve disease, 5) seronegative arthritis, 6) ankylosing spondylitis, and 7) rheumatoid arthritis.

Aortic Root Dilatation

Various conditions have been associated with aortic root dilatation. Advancing age is 1 factor; hypertension accelerates this process. Aortic regurgitation associated with age or hypertension is common and usually mild. Marfan syndrome may cause progressive dilatation of the aortic root and ascending aorta. Medical therapy, aimed at slowing the aortic dilatation rate and reducing complications, includes β-adrenergic blocker therapy. Angiotensin receptor blockers may be a treatment, although data are inconclusive about their use for adults with aortic root dilatation. When the aortic diameter reaches 5.0 to 5.5, it should be replaced. Syphilis is an uncommon cause of aortic regurgitation and usually causes aortic root dilatation above the sinuses, sparing the sinuses. Syphilis is associated with aortic root calcium on chest radiography.

Table 10.2 • Aortic Regurgitation: Symptoms and Findings on Examination

	Aortic Regurgitation	
Characteristics	**Acute**	**Chronic**
Symptoms	Pulmonary edema	Dyspnea
	Shock	Fatigue
	Arrhythmia	Exercise intolerance
	Chest pain	Night sweats
	Dissection, RCA infarct	Palpitations
Examination	Faint short murmur	Peripheral pulses
		Quincke and Duroziez signs, pistol-shot pulse
		Enlarged, diffuse, hyperdynamic LV
		Murmur
		LSB—valve cause
		RSB—root cause
Chest radiography	Wide mediastinum	Enlarged heart
	Pulmonary edema	Enlarged aorta
Electrocardiography	Low voltage (if pericardial effusion)	LVH
	ST elevation II, III, F (if aortic dissection into RCA)	

Abbreviations: LSB, left sternal border; LV, left ventricle; LVH, left ventricular hypertrophy; RCA, right coronary artery; RSB, right sternal border.

Symptoms

The symptoms of *acute* aortic regurgitation are extreme: pulmonary edema, shock, and often, chest pain (in the clinical setting of aortic dissection). Symptoms of *chronic* aortic regurgitation can develop insidiously because of compensatory mechanisms of the heart. The most common symptoms of *severe* aortic regurgitation are fatigue, dyspnea, palpitations, and exertional angina.

Physical Examination

Severe aortic regurgitation is associated with widened pulse pressure that leads to high systolic blood pressure and very low diastolic blood pressure. The widened pulse pressure leads to physical findings, which include a bounding, rapidly collapsing Corrigan pulse; bisferiens pulse (may be present); de Musset head nodding; Duroziez sign (systolic and diastolic ["to-and-fro"] murmur on gentle compression with stethoscope) over the femoral artery; and Quincke sign (pulsatile capillary nail bed). Müller sign (systolic pulsations of the uvula) is often noted. The LV impulse is diffuse and enlarged, displaced inferior-laterally, and hyperdynamic. The apical impulse is often displaced downward. A diastolic decrescendo murmur is heard at the left or the right sternal border, and the second heart sound may be paradoxically split because of increased LV volume. Aortic regurgitation murmurs are some of the hardest murmurs to appreciate and must be listened for in a quiet setting and in multiple patient positions, especially with the patient seated, leaning forward, and at end expiration.

Murmur duration is related to the rate of pressure equilibration between the aorta and the left ventricle. Aortic regurgitation with physiologic diastolic pressures results in a holodiastolic murmur. The shorter the aortic regurgitation murmur, the faster the pressure equilibration is and thus the more severe the aortic regurgitation (higher LV end-diastolic pressure). Murmur loudness does not correlate with aortic regurgitation severity, particularly in acute aortic regurgitation (eg, with dissection). A systolic flow murmur is common because of the increased ejection volume. It does not necessarily indicate aortic stenosis.

Diagnosis

Acute aortic regurgitation may not be identified on bedside examination if a patient presents with little or no murmur.

Table 10.3 • Natural History of Severe Aortic Regurgitation

Status of Patient	% of Patients per Year
Asymptomatic with normal LV systolic function	
Progression to symptoms or LV dysfunction	<6
Progression to asymptomatic LV dysfunction	<3.5
Sudden death	<0.2
Asymptomatic with LV dysfunction	
Progression to cardiac symptoms	>25
Symptomatic	
Mortality rate	>10

Abbreviation: LV, left ventricular.

From Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, et al; 2006 Writing Committee Members; American College of Cardiology/American Heart Association Task Force. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2008 Oct 7;118(15):e523-661. Epub 2008 Sep 26; used with permission.

Electrocardiography often shows LV hypertrophy. Echocardiography is best suited to gather the important functional and hemodynamic data needed to make management decisions in aortic regurgitation. Because chronic aortic regurgitation has a long, silent, well-compensated natural history, the patient's LV size, aortic root size and morphologic characteristics, valve morphologic characteristics, and LV function (ejection fraction) should be monitored with echocardiography.

Chest radiography shows an enlarged cardiac shadow and prominence of the left ventricle in a leftward and inferior pattern. The aorta also may be enlarged, especially in Marfan syndrome. Table 10.3 outlines the natural history of severe aortic regurgitation.

Treatment

Acute severe aortic regurgitation is a surgical emergency. If untreated, severe pulmonary congestion, arrhythmias, and circulatory collapse will develop. As a bridge to operation, nitroprusside is administered to reduce peripheral resistance and encourage forward flow; inotropic agents to augment cardiac output may be considered. An intra-aortic balloon pump is contraindicated because it will worsen regurgitation.

Key Definition

Chronic aortic regurgitation: ***combined volume and pressure overload on the left ventricle.***

Chronic aortic regurgitation is a combined volume and pressure overload on the left ventricle. The left ventricle compensates by dilating and increasing compliance. Patients with aortic regurgitation may be asymptomatic for decades. The development of symptoms usually reflects LV dysfunction, and survival is limited (10% annual mortality rate) unless surgical intervention is necessarily prompt. Medical management (ie, angiotensin-converting enzyme inhibitor or nifedipine) slows ventricular dilatation in patients with severe aortic regurgitation and may help delay operation. Compensation is not maintained indefinitely, and eventually LV filling pressure increases, coronary flow reserve diminishes, and LV dysfunction develops insidiously. Angina, even in the absence of epicardial coronary stenosis, may be present as a result of supply-and-demand mismatch.

Asymptomatic LV dysfunction may develop in a subset of patients. Several factors have been suggested to prompt surgical intervention before LV dysfunction develops: an end-systolic dimension more than 50 mm, an end-diastolic dimension more than 65 mm, or an ejection fraction of 50% or less (Figure 10.2). Asymptomatic patients with a dilated left ventricle must be monitored carefully. Evidence of LV systolic dysfunction at rest, progressive diastolic dysfunction, or rapidly progressive LV dilatation should prompt surgical treatment. The ability to repair (rather than replace) the valve may favor earlier operation (before LV dilatation has occurred).

KEY FACTS

- ✓ Bicuspid aortic valve—may be associated with coarctation of the aorta in approximately 10% of patients; conversely, if coarctation is noted, the chance of BAV is 30% to 50%
- ✓ In hemodynamically significant aortic stenosis—arterial pulse is parvus (small and difficult to feel) and tardus (delayed)
- ✓ Causes of valvular aortic regurgitation—1) congenital bicuspid valve, 2) rheumatic fever, 3) endocarditis, 4) degenerative aortic valve disease, 5) seronegative arthritis, 6) ankylosing spondylitis, and 7) rheumatoid arthritis
- ✓ Acute severe aortic regurgitation—
    - a surgical emergency that, if untreated, leads to severe pulmonary congestion, arrhythmias, and circulatory collapse
    - as a bridge to operation for the condition, nitroprusside may be considered to reduce peripheral resistance and encourage forward flow or inotropic agents to augment cardiac output

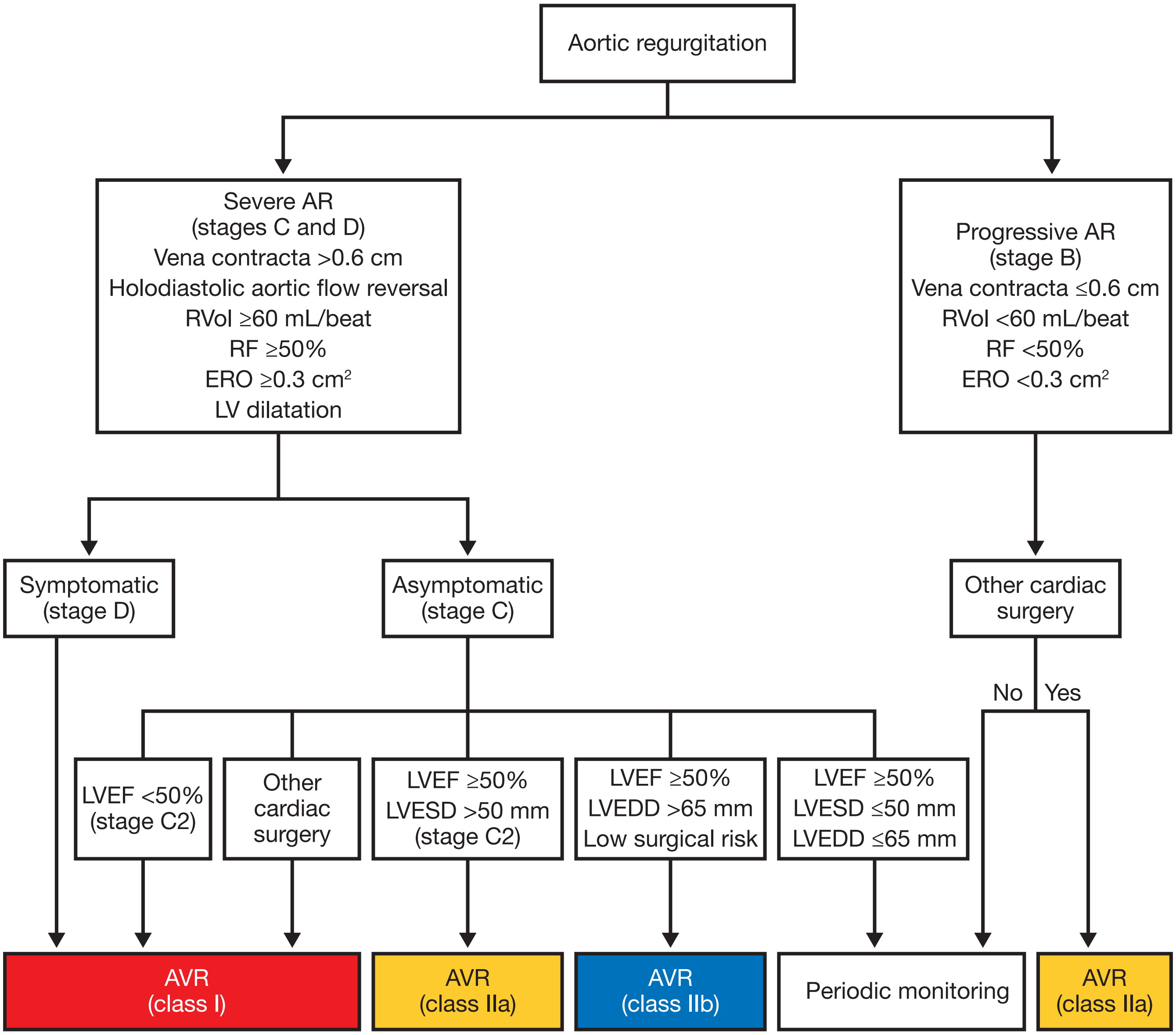

Aortic regurgitation
Severe AR (stages C and D) Vena contracta >0.6 cm Holodiastolic aortic flow reversal RVol ≥60 mL/beat RF ≥50% ERO ≥0.3 cm²
LV dilatation
Progressive AR (stage B) Vena contracta ≤0.6 cm RVol <60 mL/beat RF <50% ERO <0.3 cm²
Symptomatic (stage D)
Asymptomatic (stage C)
Other cardiac surgery
No
Yes
LVEF <50% (stage C2)
Other cardiac surgery
LVEF ≥50% LVESD >50 mm (stage C2)
LVEF ≥50% LVEDD >65 mm Low surgical risk
LVEF ≥50% LVESD ≤50 mm LVEDD ≤65 mm
AVR (class I)
AVR (class IIa)
AVR (class IIb)
Periodic monitoring
AVR (class IIa)

Figure 10.2. *Indications for Aortic Valve Replacement (AVR) in Chronic Aortic Regurgitation (AR). In contrast to AVR, valve repair may be appropriate in selected patients. ERO indicates effective regurgitant orifice; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; RF, regurgitant fraction; RVol, regurgitant volume.*

(From Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al; ACC/AHA Task Force Members. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 10;129[23]:e521-643. Epub 2014 Mar 3. Errata in: Circulation. 2014 Jun 10;129[23]:e651. Circulation. 2014 Sep 23;130[13]:e120. Dosage error in article text; used with permission.)

Mitral Stenosis

Etiologic and Pathophysiologic Factors

Rheumatic fever is the cause of rheumatic heart disease, which leads to leaflet thickening with fusion of the commissures and, later, calcification. These effects result in mitral stenosis, and prophylaxis against rheumatic fever is therefore strongly recommended. Mitral stenosis results in obstruction of blood flow from the left atrium to the left ventricle, preventing proper diastolic filling and leading to pulmonary congestion. The differential diagnosis of mitral stenosis, such as calcified mitral valve annulus, is becoming more common in the aging US population. Other rare causes of mitral stenosis are cor triatriatum, heart disease due to radiation, and other inflammatory or autoimmune diseases.

Symptoms

Symptoms of mitral stenosis usually develop decades after rheumatic fever. The murmur of mitral stenosis is apparent on physical examination about 10 years after rheumatic fever. After another decade, symptoms develop—usually dyspnea and later orthopnea with paroxysmal nocturnal dyspnea, which can be insidious. Atrial fibrillation leads to deterioration of clinical status. Hemoptysis and pulmonary hypertension with signs of right-sided heart failure (ie, ascites and peripheral edema) are late manifestations. The risk of systemic emboli is increased, especially with the development of atrial fibrillation. Commonly, patients with previously undiagnosed mitral stenosis initially present with an embolic event or atrial fibrillation.

Physical Examination

The first heart sound in mitral stenosis is loud as long as the leaflets are pliable. The shorter the interval from the aortic valve component to the opening snap, the more severe the mitral stenosis. An opening snap occurs only with a pliable valve, and it disappears after the valve calcifies. The stenosis is mild if this interval is more than 90 milliseconds, moderate if 80 milliseconds, and severe if less than 60 milliseconds. The diastolic murmur is a low-pitched holodiastolic rumble, heard best at the apex with the bell of the stethoscope and with the patient in the left lateral decubitus position. The murmur may have presystolic accentuation if sinus rhythm is present. Right ventricular lift and increased pulmonic valve component are associated with pulmonary hypertension.

Diagnosis

Electrocardiography can show left atrial enlargement, P mitrale (notched *P* wave in leads I and II with duration ≥0.12 millisecond due to characteristic left atrial enlargement), and right ventricular hypertrophy. Chest radiography (Figure 10.3) shows straightening of the left heart border with a large left atrial shadow and dilated upper lobe pulmonary veins. With pulmonary hypertension, the central pulmonary arteries become prominent. In severe stenosis, pulmonary congestion characterized by Kerley B lines may be present, indicating a pulmonary wedge pressure of more than 20 mm Hg.

Two-dimensional and Doppler echocardiography is the test of choice to diagnose mitral stenosis and determine its severity. Information is gained about valve gradient and valve area (Table 10.4), and pulmonary artery pressures can be assessed noninvasively. Cardiac catheterization is usually unnecessary unless the coronary arteries need to be studied or the echocardiographic findings do not concur with the clinical situation. Severe stenosis usually correlates with a mean gradient of 12 mm Hg or more, but the mean gradient varies with the heart rate. Accurate calculation of valve area by echocardiographic parameters is indicated to determine the true degree of mitral stenosis severity.

Treatment

Because mitral stenosis represents obstruction to diastolic filling, anything that shortens diastolic filling time will worsen the severity and symptoms of the disease (eg, tachycardia, atrial fibrillation, exercise). Therefore, β-adrenergic blockers and calcium channel blockers can be used to slow heart rate and improve LV filling. Salt restriction and diuretic therapy are useful for early symptoms.

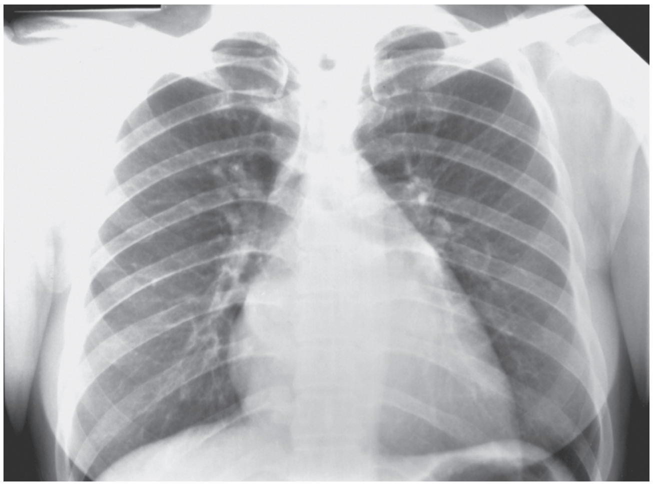


Figure 10.3. Chest Radiograph of a Patient With Severe Mitral Stenosis. The straight left heart border, prominent pulmonary artery, large left atrium, right ventricular contour, and pulmonary venous hypertension are typical findings.

The left ventricle is unaffected in mitral stenosis. However, it is small, vigorous, and possibly underfilled (reduced preload) in late mitral stenosis. Intervention on the mitral valve is not recommended until a patient has symptoms of exertional dyspnea, pulmonary edema, or moderate pulmonary hypertension. Marked volume overload of the left atrium leads to increased stroke risk because of stagnation of blood flow and thrombus formation. Atrial fibrillation is frequent and intermittent in the early stages. Intermittent screening may be warranted, and anticoagulation should be considered early.

After symptoms are present (Figure 10.4), treatment is with either surgical valve replacement or percutaneous balloon valvuloplasty. Percutaneous mitral valve balloon valvuloplasty is first-line therapy when mitral valve leaflets are pliable, noncalcified regurgitation is minimal, and no left atrial clot is present. Valve

Table 10.4 • Severity of Mitral Stenosis by Valve Area, Gradient, and Pulmonary Pressure

Severity	Valve Area, cm^2	Mean Gradient, mm Hg	Systolic PAP, mm Hg
Mild	>1.5	<6	Normal
Moderate	≤1.5	6-11	≤50
Severe	<1	≥12	>50

Abbreviation: PAP, pulmonary artery pressure.

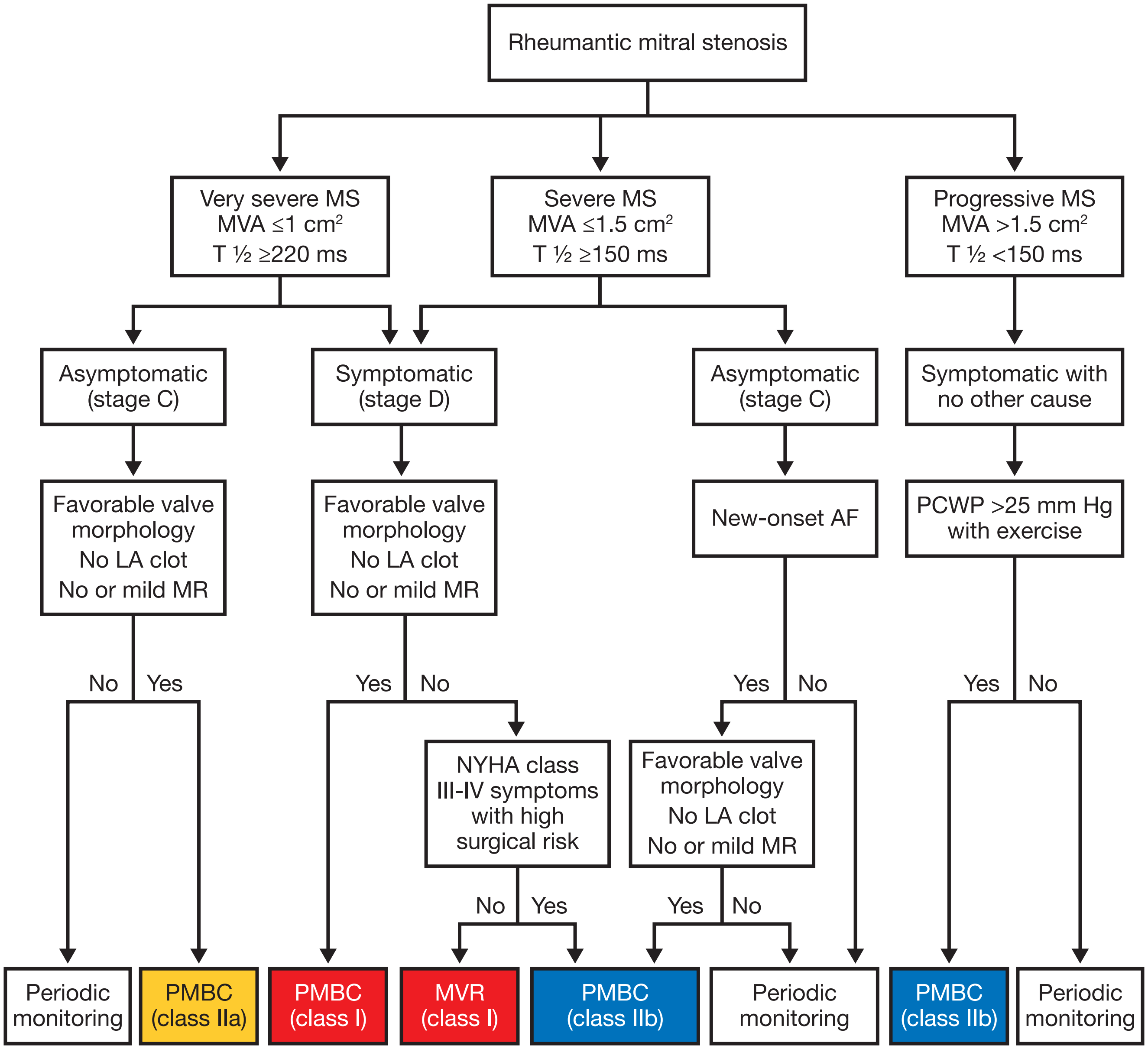

Rheumantic mitral stenosis
Very severe MS
MVA ≤1 cm²
T ½ ≥220 ms
Severe MS
MVA ≤1.5 cm²
T ½ ≥150 ms
Progressive MS
MVA >1.5 cm²
T ½ <150 ms
Asymptomatic (stage C)
Symptomatic (stage D)
Asymptomatic (stage C)
Symptomatic with no other cause
Favorable valve morphology
No LA clot
No or mild MR
Favorable valve morphology
No LA clot
No or mild MR
New-onset AF
PCWP >25 mm Hg with exercise
No
Yes
Yes
No
Yes
No
Yes
No
NYHA class III-IV symptoms with high surgical risk
Favorable valve morphology
No LA clot
No or mild MR
No
Yes
Yes
No
Periodic monitoring
PMBC (class IIa)
PMBC (class I)
MVR (class I)
PMBC (class IIb)
Periodic monitoring
PMBC (class IIb)
Periodic monitoring

Figure 10.4. *Indications for Intervention for Rheumatic Mitral Stenosis (MS). AF indicates atrial fibrillation; LA, left atrial; MR, mitral regurgitation; MVA, mitral valve area; MVR, mitral valve surgery (repair or replacement); NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PMBC, percutaneous mitral balloon commissurotomy; T ½, pressure half-time.*

(From Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al; ACC/AHA Task Force Members. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 10;129[23]:e521-643. Epub 2014 Mar 3. Errata in: Circulation. 2014 Jun 10;129[23]:e651. Circulation. 2014 Sep 23;130[13]:e120. Dosage error in article text; used with permission.)

replacement is done when symptoms are more severe because of its associated morbidity and death. Intervention for mitral stenosis is indicated by 1) severity of the valvular disease, 2) symptoms of exertional dyspnea, 3) development of atrial fibrillation, and 4) pulmonary capillary wedge pressure more than 25 mm Hg with exercise.

Mitral Regurgitation

Etiologic and Pathophysiologic Factors

The mitral valve is a complex structure, and regurgitation can result from abnormalities of 3 anatomical locations: leaflet, tensor apparatus (chordal and papillary muscles), and myocardium. Typically, mitral regurgitation is separated into either **primary**

Table 10.5 • Anatomical Types of Mitral Regurgitation

	Clinical Presentation	
Anatomical Type	**Chronic**	**Acute or Subacute**
Leaflets	Rheumatic Prolapse Annular calcification Connective tissue disease Congenital cleft Drug-related	Infective endocarditis
Tensor apparatus (chordal and papillary muscles)	Prolapse	Rupture of chordae Myocardial infarction Papillary muscle rupture
Myocardium	Regional ischemia or infarctions Dilated cardiomyopathy Hypertrophic cardiomyopathy	

Modified from McGoon MD, Schaff HV, Enriquez-Sarano M, Fuster V, Callahan MJ. Mitral regurgitation. In: Guiliani ER, Gersh BJ, McGoon MD, Hayes DL, Schaff HV, editors. Mayo Clinic practice of cardiology. 3rd ed. St. Louis (MO): Mosby; c1996. p. 1450-69; used with permission of Mayo Foundation for Medical Education and Research.

mitral regurgitation where there is an organic structural cause to the valve or **secondary** mitral regurgitation due to functional causes such as LV problems that result in mitral valve incompetence. Common primary causes of mitral regurgitation include mitral valve prolapse syndrome and myxomatous degeneration, infective endocarditis, collagen vascular disease, and rheumatic heart disease. Secondary or functional mitral regurgitation is due to conditions that affect the left ventricle, such as ischemia and nonischemic dilated cardiomyopathy. When LV dilatation is present, it leads to reduced closure and tenting of the mitral valve and thereby causes incompetence and regurgitation. In the case of ischemic mitral regurgitation, the posterior medial papillary muscle with its single blood supply (compared with anterolateral with its dual blood supply) is more susceptible. Similar to aortic regurgitation, mitral regurgitation may be acute or chronic (Table 10.5). Acute onset of mitral regurgitation may result in hemodynamic compromise and pulmonary edema, necessitating immediate stabilization and intervention.

Symptoms

Chronic mitral regurgitation causes LV volume overload with reduced afterload. Given time, the left ventricle compensates by increasing the stroke volume. A long asymptomatic phase is thus possible. The most common symptoms are fatigue, dyspnea (due to increased left atrial pressure), and pulmonary edema. Symptoms often worsen with atrial fibrillation.

Physical Examination

Findings of mitral regurgitation include a palpable rapid filling wave and a diffuse and hyperdynamic LV impulse, which may be visible. The second heart sound may be obliterated and a holosystolic murmur present. There may be a third heart sound (or a third heart sound and a flow rumble) and a fourth heart sound. A third heart sound with a low-pitched early diastolic rumble indicates severe regurgitation; it represents a volume murmur, but coexisting mitral stenosis needs to be ruled out.

In acute mitral regurgitation, the murmur may be short because of increased left atrial pressure. In severe mitral regurgitation, the carotid upstroke may appear parvus because of the low forward stroke volume, but not tardus (which is classic for aortic stenosis). The LV apex may be palpable with systole, inferior-laterally displaced, enlarged, but either tapping if compensated or diffuse and soft if LV decompensated. The cause of mitral regurgitation may be suspected by the radiation of the auscultated murmur. A murmur due to a rupture of the anterior leaflet chordae leads to a posteriorly directed jet of mitral regurgitation and a murmur that radiates to the axilla and back. With posterior leaflet chordae rupture, the murmur radiates to the sternum and possibly the carotid arteries.

Diagnosis

Chest radiography may first show a dilated left atrium and, as mitral regurgitation increases, dilatation of the left ventricle. Echocardiography is a useful tool to assess the cause of the mitral regurgitation (primary or secondary), the regurgitation amount, and the LV function and size, which will influence the timing of intervention. A low or low-normal ejection fraction suggests substantial ventricular dysfunction. It is important to monitor patients closely to determine the optimal timing of surgical intervention.

Treatment

No medical treatment of mitral regurgitation is universally accepted. The onset of clinical symptoms warrants intervention (mitral valve repair or replacement). Treatment typically depends on assessment of the cause of the mitral regurgitation—primary or secondary. Asymptomatic patients with normal or hyperdynamic ejection fraction can continue to have regular observation. Operation should be considered for symptomatic patients (preoperative LV function considerably influences the postoperative outcome). Because afterload is increased when the mitral valve is replaced, LV function may actually deteriorate after mitral valve repair or replacement. In most patients, ejection fraction decreases approximately 10% after mitral valve repair or replacement.

In mildly symptomatic patients, operation may be considered, particularly when serial examinations show progressive cardiac enlargement. Earlier operation may be indicated for patients who are candidates for mitral valve repair rather than replacement, especially when the ejection fraction is less than 60% or the LV end-systolic dimension is more than 40 mm (Figure 10.5).

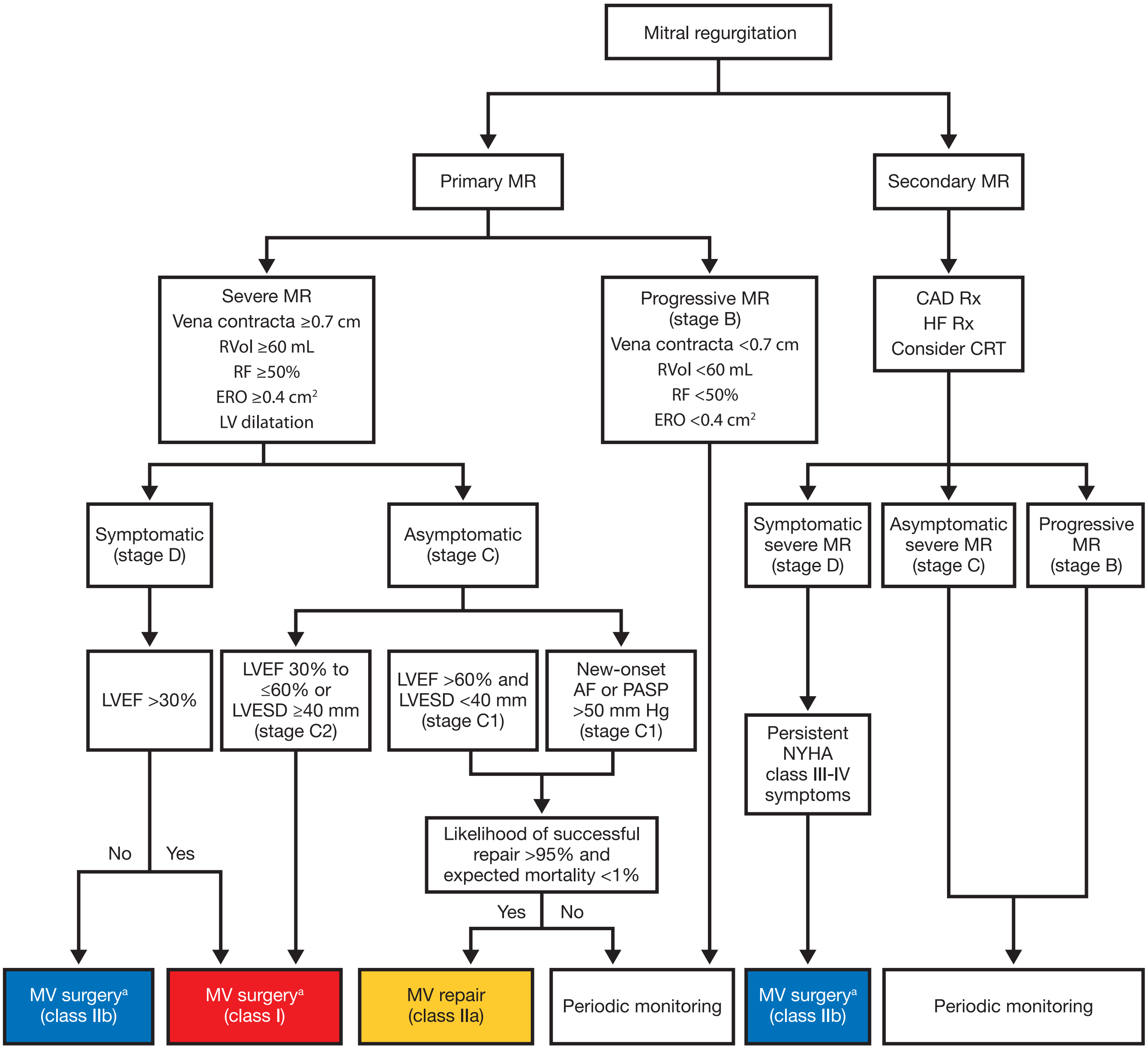

Mitral regurgitation
Primary MR
Secondary MR
Severe MR Vena contracta ≥0.7 cm RVol ≥60 mL RF ≥50% ERO ≥0.4 cm² LV dilatation
Progressive MR (stage B) Vena contracta <0.7 cm RVol <60 mL RF <50% ERO <0.4 cm²
CAD Rx HF Rx Consider CRT
Symptomatic (stage D)
Asymptomatic (stage C)
Symptomatic severe MR (stage D)
Asymptomatic severe MR (stage C)
Progressive MR (stage B)
LVEF >30%
LVEF 30% to ≤60% or LVESD ≥40 mm (stage C2)
LVEF >60% and LVESD <40 mm (stage C1)
New-onset AF or PASP >50 mm Hg (stage C1)
Persistent NYHA class III-IV symptoms
Likelihood of successful repair >95% and expected mortality <1%
No
Yes
Yes
No
MV surgery[a] (class IIb)
MV surgery[a] (class I)
MV repair (class IIa)
Periodic monitoring
MV surgery[a] (class IIb)
Periodic monitoring

Figure 10.5. *Indications for Surgery for Mitral Regurgitation (MR). AF indicates atrial fibrillation; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; ERO, effective regurgitant orifice; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MV, mitral valve; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVol, regurgitant volume; Rx, therapy.* [a] *Mitral valve repair is preferred over replacement when possible.*

(From Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al; ACC/AHA Task Force Members. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 10;129[23]:e521-643. Epub 2014 Mar 3. Errata in: Circulation. 2014 Jun 10;129[23]:e651. Circulation. 2014 Sep 23;130[13]:e120. Dosage error in article text; used with permission.)

KEY FACTS

- ✓ Mitral stenosis—2-dimensional and Doppler echocardiography is the test of choice to diagnose the condition and determine its severity
- ✓ Intervention on mitral valve—is not recommended until there are symptoms of exertional dyspnea, pulmonary edema, or moderate pulmonary hypertension
- ✓ Mitral regurgitation—no universally accepted medical treatment
- ✓ In patients with mitral regurgitation who are candidates for mitral valve repair rather than replacement—earlier operation may be indicated, especially with ejection fraction <60% or LV end-diastolic dimension >40 mm

Mitral Valve Prolapse

Pathophysiologic Factors and Natural History

Mitral valve prolapse is the most common cause of both valvular heart disease and mitral regurgitation in the United States. ***Mitral valve prolapse*** refers to a systolic billowing of 1 or both mitral leaflets into the left atrium with or without mitral regurgitation. In patients with mitral valve prolapse, as with other causes of mitral regurgitation, the degree of left atrial and LV dilatation depends on the severity of the mitral regurgitation.

Key Definition

Mitral valve prolapse: *systolic billowing of 1 or both mitral leaflets into the left atrium with or without mitral regurgitation.*

In Marfan syndrome, the supporting apparatus is often involved with dilatation of the mitral annulus in addition to elongation of the chordae and redundant leaflets—abnormalities leading to mitral valve prolapse. Other valves also may be involved with the same myxomatous degeneration, which causes tricuspid valve prolapse (occurring in approximately 40% of patients with mitral valve prolapse), pulmonic valve prolapse (about 10%), and aortic valve prolapse (2%). Other connective tissue disorders may be associated with mitral valve prolapse.

Mitral valve prolapse syndrome has a benign course in most patients. A risk exists of ruptured mitral valve chordae, which may lead to acute decompensation. Infective endocarditis is a serious complication of mitral valve prolapse, although the overall incidence is low. There is a low risk of sudden cardiac death (Figure 10.6).

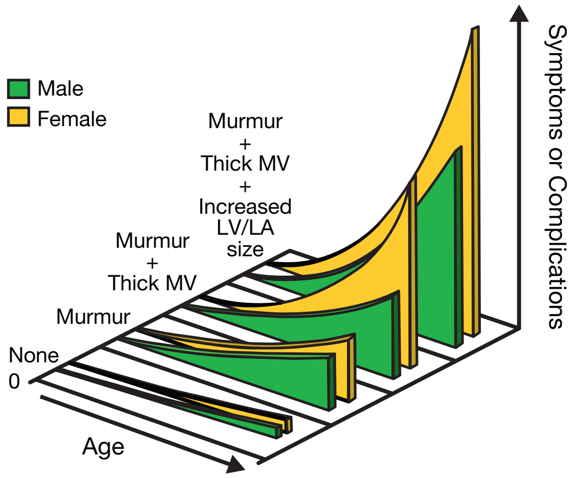


Figure 10.6. Risk Factors for Complications in Mitral Valve (MV) Prolapse. LA indicates left atrial; LV, left ventricular.

(From Boudoulas H, Kolibash AJ Jr, Wooley CF. Mitral valve prolapse: a heterogeneous disorder. Primary Cardiol. 1991;17[2]:29-43; used with permission.)

Physical Examination

Mitral valve prolapse is usually diagnosed with cardiac auscultation in asymptomatic patients or incidentally on echocardiography. The classic auscultatory finding is the midsystolic click, a high-pitched sound of short duration. Multiple clicks may be heard. Clicks result from sudden tensing of the mitral valve apparatus as the leaflets prolapse into the left atrium during systole. The midsystolic click is frequently followed by a mid-to-late systolic murmur that is high-pitched, musical, or honking and is often loudest at the cardiac apex. The character and intensity of the clicks and the murmur vary with the left ventricle loading conditions. Dynamic auscultation helps establish the diagnosis. Changes in LV end-diastolic volume result in changes in the timing of the clicks and murmur. When end-diastolic volume is decreased (eg, with standing), the critical volume is achieved earlier in systole and the click-murmur complex occurs earlier after the first heart sound. In contrast, any maneuver that augments the volume of blood in the ventricle (eg, squatting), reduces myocardial contractility, or increases LV afterload also lengthens the time from onset of systole to initiation of mitral valve prolapse, and the systolic click or murmur moves toward the second heart sound (Figure 10.7).

Diagnosis

Results of electrocardiography most often are normal, although 24-hour ambulatory electrocardiographic recordings or event monitors may be useful for documenting arrhythmias. Echocardiography is the most useful noninvasive test for defining mitral valve prolapse. The definition includes more than 2 mm of posterior displacement of 1 or

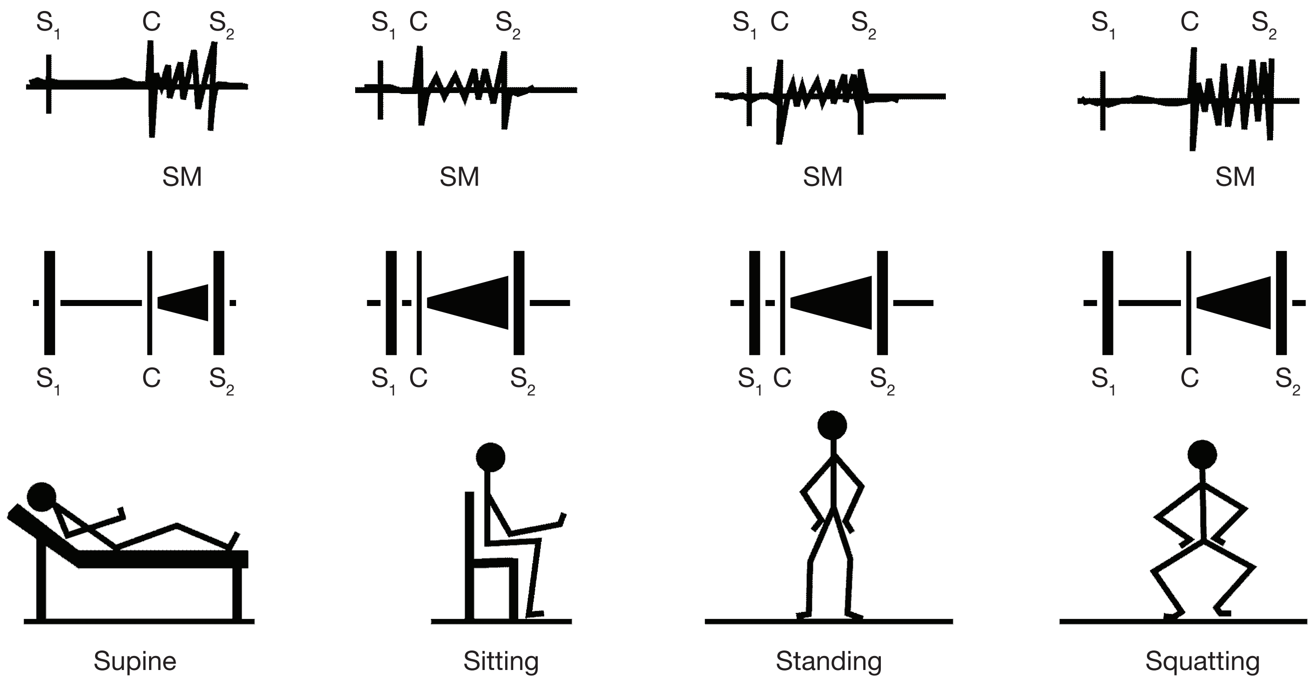


Figure 10.7. *Auscultation Findings in Mitral Valve Prolapse. C indicates click;* S_1, S_2, *heart sound (first, second); SM, systolic murmur;* ◀, *murmur.*

both leaflets into the left atrium. All patients with mitral valve prolapse should have initial echocardiography to establish the diagnosis, stratify risk, and define possible associated lesions (eg, atrial septal defect). Serial echocardiograms are not necessary in asymptomatic patients with mitral valve prolapse. Echocardiographic follow-up should be done if the patient has clinical indications of progression or moderate or greater mitral regurgitation.

Treatment

Reassurance is a major part of therapy for patients with mitral valve prolapse because most are asymptomatic and do not have a high-risk profile. A normal lifestyle and regular exercise are encouraged. Patients should be educated about when to seek medical advice (with worsening symptoms). Subacute bacterial endocarditis prophylaxis is no longer indicated for mitral valve prolapse without a history of endocarditis.

Common symptoms include palpitations, chest pain that rarely resembles classic angina pectoris, dyspnea, and fatigue.

Asymptomatic patients with mitral valve prolapse and mild mitral regurgitation can be evaluated clinically every 3 to 5 years. Serial echocardiography is necessary only for patients who have high-risk characteristics on the initial echocardiogram or have a change in clinical status.

Surgery may be required in a small subset of patients. The thickened redundant mitral valve often can be repaired rather than replaced; repair has a low operative mortality rate and excellent short- and long-term results. Repair is often sufficient for patients who have a flail mitral leaflet due to rupture or marked elongation of the chordae tendineae. Recommendations for surgery for patients with mitral valve prolapse and mitral regurgitation are the same as those for patients with other forms of severe mitral regurgitation.

KEY FACTS

- ✓ Mitral valve prolapse—the most common cause of both valvular heart disease and mitral regurgitation in the United States
- ✓ Mitral valve prolapse—all patients should have initial echocardiography to establish diagnosis, stratify risk, and define possible associated lesions (eg, atrial septal defect)
- ✓ In asymptomatic patients with mitral valve prolapse—serial echocardiography is not necessary
- ✓ In patients with mitral valve prolapse and clinical indications of progression—echocardiographic follow-up should be done

Tricuspid Stenosis

The cause of tricuspid stenosis is almost always rheumatic, and it is never an isolated lesion. Carcinoid syndrome may cause tricuspid valve retraction and a relative stenosis (which usually causes worse tricuspid regurgitation), and in rare cases, atrial tumors may be the cause.

Tricuspid Valve Prolapse

This may occur in isolation or may be associated with other connective tissue abnormalities. The tricuspid valve may prolapse or become flail as a result of trauma or endocarditis (commonly fungal or staphylococcal in persons addicted to drugs).

Tricuspid Regurgitation

Mild tricuspid regurgitation is relatively common, occurring in up to 90% of the population. Serious tricuspid regurgitation may be primary to a valvular apparatus abnormality or secondary to alternation in valve geometry related to changes in the right ventricular size or pressure.

Physical Examination

Findings on physical examination are jugular venous distention with a prominent *v* wave, a prominent right ventricular impulse, a pansystolic murmur at the left sternal edge, possibly a right-sided third heart sound, peripheral edema, ascites, and hepatomegaly.

Surgical Therapy

The tricuspid valve can be repaired or replaced surgically. Tricuspid annuloplasty may be helpful when regurgitation is caused by right ventricular dilatation. On average, biologic prostheses in the tricuspid position do not degenerate as quickly as left-heart prostheses (Figure 10.8).

Prosthetic Valves

Bioprosthetic Valves

Tissue valves, or bioprostheses, include autografts (usually the patient's own pulmonary valve), homografts (aortic or pulmonary valves from human cadavers), and heterografts (either porcine valves or bovine pericardial tissue attached to a metal frame). Bioprosthesis implantation traditionally required open heart surgery, but in recent years, patients deemed at too high a risk for surgical aortic valve replacement are increasingly undergoing transcatheter aortic valve replacement with implantation via a transfemoral or transapical catheter. Transcatheter pulmonary valve replacement for patients with congenital heart disease is also increasingly common. Currently, no approved transcatheter mitral or tricuspid valve replacement options are available.

Because bioprostheses are not as thrombogenic as mechanical valves, most patients in sinus rhythm do not require anticoagulation after the first 3 to 6 months postimplantation unless they have additional risk factors, such as atrial fibrillation. Tissue valves degenerate and calcify, particularly in young patients or patients who have disordered calcium metabolism (eg, end-stage renal disease). Approximately 50% of patients with a bioprosthesis require redo valve replacement at 10 to 15 years because of structural deterioration. Prostheses in the tricuspid and pulmonary positions tend to last longer than those in left heart positions. Aortic bioprostheses are generally more durable than mitral bioprostheses. Prosthesis failure can be detected with clinical evaluation and 2-dimensional and Doppler echocardiography.

Mechanical Valves

Older-generation mechanical prostheses, including the caged ball (eg, Starr-Edwards) and tilting disk (eg, Medtronic-Hall), were durable but thrombogenic. These prosthesis types are no longer manufactured, but because they are durable, many patients still have them in place. The newer-generation bileaflet mechanical valves (eg, St. Jude Medical) are less thrombogenic than prior models, but they still pose a risk of thromboembolism and necessitate long-term anticoagulation. Vitamin K antagonists (eg, warfarin) are the only systemic anticoagulants approved for mechanical heart valves. New direct oral anticoagulants should not be used for prosthetic valve; anticoagulant therapy with oral direct thrombin inhibitors or anti-Xa agents should not be used for mechanical valve prostheses because of increased risk of valve thrombosis. The 2014 American Heart Association/American College of Cardiology (AHA/ACC) Guideline for the Management of Patients With Valvular Heart Disease (Circulation. 2014 Jun 10;129[23]:e521-643) recommends a single target international normalized ratio for therapeutic anticoagulation. All patients with mechanical heart valves should be given low-dose aspirin in addition to anticoagulation agents (Figure 10.9). Dual antiplatelet therapy with aspirin and a thienopyridine (eg, clopidogrel) is not an acceptable substitute for antiplatelet plus anticoagulant therapy for these patients.

Bridging Therapy

Continuation of anticoagulation with a therapeutic international normalized ratio is recommended for patients with mechanical prostheses in any position who undergo minor procedures (eg, dental extractions, cataract removal) in which bleeding can be controlled easily. Temporary interruption of anticoagulation without bridging therapy for surgical or other invasive procedures is recommended for patients with bileaflet mechanical aortic valve prostheses who have no additional risk factors for thrombosis (ie, atrial fibrillation or flutter, history of stroke, LV ejection fraction <30%, or history of thromboembolism or hypercoagulable state). Bridging anticoagulation with either intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin is recommended for patients undergoing invasive or surgical procedures who have any of the following clinical situations: 1) mechanical aortic prosthesis and any thromboembolic risk factor, 2) older-generation mechanical aortic prosthesis, or 3) any type of mechanical mitral valve prosthesis. Aspirin therapy for all patients with prosthetic heart valves should be continued without interruption unless bleeding risk is considered prohibitive.

Infective Endocarditis Prophylaxis

Patients with any type of prosthetic heart valve have a high risk of infective endocarditis. Antibiotic therapy is recommended

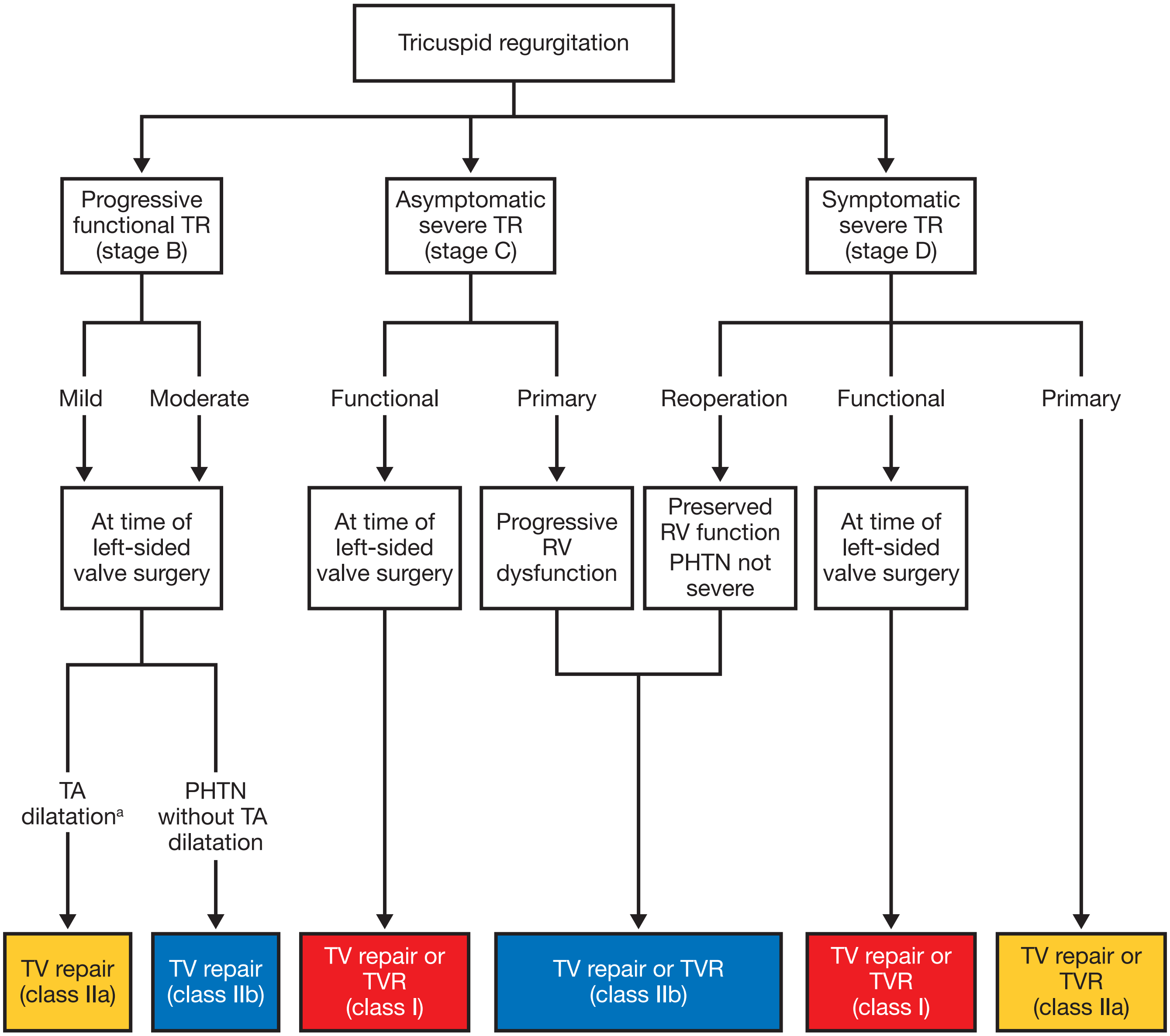

Tricuspid regurgitation
Progressive functional TR (stage B)
Asymptomatic severe TR (stage C)
Symptomatic severe TR (stage D)
Mild
Moderate
Functional
Primary
Reoperation
Functional
Primary
At time of left-sided valve surgery
At time of left-sided valve surgery
Progressive RV dysfunction
Preserved RV function PHTN not severe
At time of left-sided valve surgery
TA dilatation[a]
PHTN without TA dilatation
TV repair (class IIa)
TV repair (class IIb)
TV repair or TVR (class I)
TV repair or TVR (class IIb)
TV repair or TVR (class I)
TV repair or TVR (class IIa)

Figure 10.8. *Indications for Surgery for Tricuspid Regurgitation (TR). PHTN indicates pulmonary hypertension; RV, right ventricular; TA, tricuspid annular; TV, tricuspid valve; TVR, tricuspid valve replacement. [a] Dilatation is defined as more than 40 mm on transthoracic echocardiography (>21 mm/m^2) or more than 70 mm on direct intraoperative measurement.*

(From Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al; ACC/AHA Task Force Members. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 10;129[23]:e521-643. Epub 2014 Mar 3. Errata in: Circulation. 2014 Jun 10;129[23]:e651. Circulation. 2014 Sep 23;130[13]:e120. Dosage error in article text; used with permission.)

before all dental procedures that involve manipulation of gingival tissue or perforation of the oral mucosa. In the absence of suspected infection, prophylaxis before gastrointestinal tract or genitourinary procedures is not recommended. Morbidity and mortality rates of patients with prosthetic valve endocarditis are higher than rates associated with native valve endocarditis.

Prosthetic Valve Complications and Dysfunction

The risk of serious complications is approximately 3% per year. Potential complications include bleeding, valve obstruction due to thrombosis or pannus, systemic embolization, structural deterioration (primarily with bioprosthesis), hemolytic anemia, perivalvular regurgitation, and infective endocarditis.

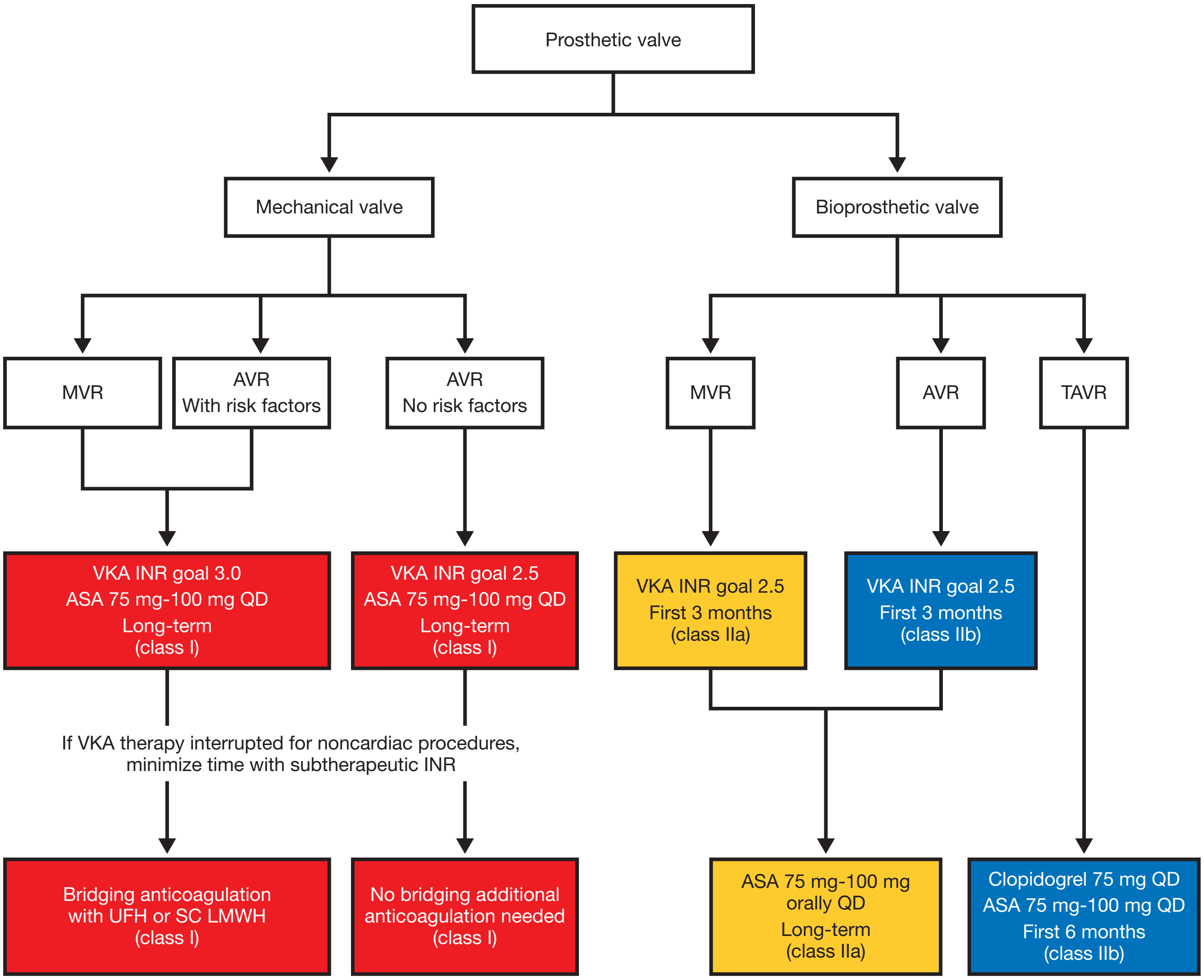

Prosthetic valve
Mechanical valve
Bioprosthetic valve
MVR
AVR With risk factors
AVR No risk factors
MVR
AVR
TAVR
VKA INR goal 3.0 ASA 75 mg-100 mg QD Long-term (class I)
VKA INR goal 2.5 ASA 75 mg-100 mg QD Long-term (class I)
VKA INR goal 2.5 First 3 months (class IIa)
VKA INR goal 2.5 First 3 months (class IIb)
If VKA therapy interrupted for noncardiac procedures, minimize time with subtherapeutic INR
Bridging anticoagulation with UFH or SC LMWH (class I)
No bridging additional anticoagulation needed (class I)
ASA 75 mg-100 mg orally QD Long-term (class IIa)
Clopidogrel 75 mg QD ASA 75 mg-100 mg QD First 6 months (class IIb)

Figure 10.9. *Anticoagulation for Prosthetic Valves. Risk factors include atrial fibrillation, previous thromboembolism, left ventricular dysfunction, hypercoagulable condition, and older-generation mechanical aortic valve replacement (AVR). ASA indicates aspirin; INR, international normalized ratio; LMWH, low-molecular-weight heparin; MVR, mitral valve replacement; QD, every day; SC, subcutaneous; TAVR, transcatheter aortic valve replacement; UFH, unfractionated heparin; VKA, vitamin K antagonist.*

(From Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al; ACC/AHA Task Force Members. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 10;129[23]:e521-643. Epub 2014 Mar 3. Errata in: Circulation. 2014 Jun 10;129[23]:e651. Circulation. 2014 Sep 23;130[13]:e120. Dosage error in article text; used with permission.)

Severe bleeding may occur in patients with mechanical prostheses, particularly patients with a supratherapeutic international normalized ratio. The annual rate of minor hemorrhage is 2% to 4% per year and of major hemorrhage, 1% to 2% per year. When life-threatening bleeding occurs, fresh frozen plasma or prothrombin concentrate may be administered.

Thrombosis may occur on both bioprosthetic and mechanical valves, particularly with inadequate anticoagulation. Thrombosis occurs most commonly with tricuspid valve prostheses. Thrombolytic therapy or surgery may be indicated when serious obstruction of left-sided prostheses occurs. The risk of systemic embolization for patients with mechanical prostheses treated appropriately with anticoagulation is approximately 1% per year. Patients with mechanical mitral valves have twice the risk of embolization as patients with mechanical aortic valves.

Hemolytic anemia may occur in patients with prosthetic heart valves, particularly in the clinical setting of a perivalvular leak. Diagnosis is based on a high degree of suspicion and on laboratory evidence of intravascular hemolysis. Surgical or catheter closure of the perivalvular leak is indicated for patients who require repeated transfusions.

Infective endocarditis may occur at any time, but the risk is highest in the first few weeks and months after valve implantation. For a detailed discussion of infective endocarditis, please refer to Chapter 47.

Serial Follow-up of Patients With Prosthetic Valves

A baseline transthoracic echocardiogram should be obtained for all patients with prosthetic heart valves shortly after valve implantation. All patients with prosthetic heart valves should have an annual clinical evaluation, including symptom assessment and physical examination. According to the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease (Circulation. 2014 Jun 10;129[23]:e521-643), patients with mechanical valves require no further echocardiographic testing if their condition remains stable with no clinical suspicion for valve dysfunction. Because of the risk of degeneration, patients with a surgically implanted bioprosthesis should undergo annual echocardiographic examinations starting 10 years after implantation, even in the absence of symptoms. Recommendations for echocardiographic follow-up of transcatheter valve replacements are evolving, but current guidelines suggest annual echocardiographic examinations.

KEY FACTS

- ✓ Tricuspid stenosis—cause is almost always rheumatic, and it is never an isolated lesion
- ✓ Carcinoid syndrome—may cause tricuspid valve retraction and a relative stenosis (usually causes worse tricuspid regurgitation), and in rare cases, atrial tumors may be the cause of the syndrome
- ✓ Bioprosthesis—not as thrombogenic as mechanical valves and thus most patients with sinus rhythm do not require anticoagulation after the first 3-6 months postimplantation unless they have additional risk factors (eg, atrial fibrillation)
- ✓ Patients who have a prosthetic heart valve of any type—
    - are at high risk for infective endocarditis
    - antibiotic therapy is recommended before all dental procedures that involve manipulation of gingival tissue or perforation of oral mucosa
    - prophylaxis is not recommended before gastrointestinal tract or genitourinary procedures in the absence of suspected infection

Congenital Heart Disease

Atrial Septal Defect

There are multiple types of atrial septal defects (Table 10.6).

Secundum Atrial Septal Defect

Secundum atrial septal defect is the most common type of atrial septal defect. Because physical examination findings are subtle and symptoms are nonspecific, patients with secundum atrial septal defect often survive to adulthood and the condition may be diagnosed for the first time later in life. The physical examination may show a fixed split second heart sound and a soft systolic murmur representing excess flow across the pulmonary valve.

Electrocardiography characteristically shows right bundle branch block and right axis deviation. Chest radiography shows pulmonary plethora, a prominent pulmonary artery, and right ventricular enlargement (Figure 10.10). Echocardiography is warranted for definitive diagnosis.

Primum Atrial Septal Defect (Partial Atrioventricular Canal Defect)

Primum atrial septal defect is a defect at the crux of the heart, with the tricuspid and mitral valves forming part of the border of the defect. It is also called *partial atrioventricular canal defect*. The mitral valve is often congenitally cleft and produces various degrees of mitral regurgitation.

Key Definition

Primum atrial septal defect: *occurs at crux of the heart; tricuspid and mitral valves form part of the border of the defect.*

On electrocardiography, findings are different from those of secundum type; left axis deviation and right bundle branch block are evident. More than 75% of patients with this type of defect have first-degree atrioventricular block. Chest radiographic findings are the same as those for secundum atrial septal defect, but left atrial enlargement due to mitral regurgitation may be present.

Sinus Venosus Atrial Septal Defect

A sinus venosus defect occurs in atrial septal tissue at the junction of the vena cava to the right atrium, most commonly the superior vena cava. It is often associated with anomalous pulmonary venous return. If transthoracic echocardiography shows right ventricular volume overload and no secundum defect, consideration should be given to sinus venosus atrial septal defect or anomalous pulmonary veins, which are more easily diagnosed with transesophageal echocardiography.

Table 10.6 • Types of Atrial Septal Defects

Type	%	Location	Associated Findings	ECG Findings
Ostium secundum	75	Fossa ovalis	None	Incomp RBBB, R axis
Sinus venosus	10	Vena cava	Anomalous PV	Incomp RBBB, ectopic P wave, R axis
Ostium primum	10-15	Lower septum	Cleft MV, Down syndrome	Incomp RBBB, L axis (LAHB)

Abbreviations: ECG, electrocardiography; Incomp, incomplete; L axis, left axis deviation; LAHB, left anterior hemiblock; MV, mitral valve; P wave, atrial depolarization wave on ECG; PV, pulmonary veins; R axis, right axis deviation; RBBB, right bundle branch block.

Treatment

Antibiotic prophylaxis is not recommended unless the patient has associated complex congenital heart disease. Patients with atrial septal defect have variable symptoms depending on the size of the shunt. Intervention should be considered in the clinical setting of hemodynamic compromise (a left-to-right shunting >30% or evidence of right-sided chamber enlargement). Surgical closure is possible for all types of atrial septal defects, but only the secundum atrial septal defect can be treated with a transcatheter device closure.

Ventricular Septal Defect

Ventricular septal defects occur in different parts of the ventricular septum, most commonly classified as either in the membranous septum or in the muscular septum. A small ventricular septal defect generally presents with a loud holosystolic murmur in an asymptomatic patient. Often, a thrill at the left sternal edge is heard, usually around the fourth interspace. Large defects result in volume loading of the left heart with left atrial and LV dilatation. They may produce a mitral diastolic flow rumble (due to increased volume) at the apex, especially when the shunt is more than 2.5:1, and may cause considerable symptoms early in life. Ventricular septal defects are usually detected in early childhood. In developed countries, the defects are usually closed early if they are thought to be clinically significant. If undiscovered until late childhood or adulthood, a large ventricular septal defect often results in pulmonary vascular disease with pulmonary hypertension (Eisenmenger syndrome) and cannot be closed (see Eisenmenger Syndrome section below).

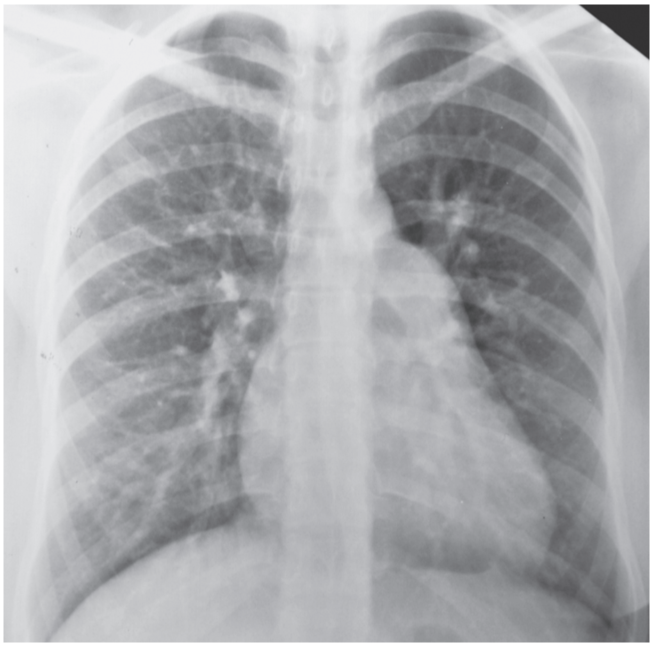


Figure 10.10. Chest Radiograph of a Patient With a Large Left-to-Right Shunt Due to a Secundum Atrial Septal Defect. Of note, cardiac enlargement is shown with right ventricular contour, prominent pulmonary artery, and pulmonary plethora.

Patent Ductus Arteriosus

The **ductus arteriosus** is a normal embryologic structure connecting the descending thoracic aorta and the pulmonary artery. This communication usually closes in the days after birth. Patency of the ductus allows a left-to-right shunt from the aorta to the pulmonary artery. A small patent ductus is likely of no clinical consequence, but a large communication results in volume loading of the left heart and pressure overload of the pulmonary circulation. A large patent ductus can result in pulmonary vascular disease and Eisenmenger syndrome (see next section). Physical examination may be notable for a continuous "machinery" murmur enveloping the second heart sound heard at the second interspace beneath the left clavicle and anteriorly along the left second intercostal space if a serious left-to-right shunt is present. A patent ductus with serious shunt can be ligated surgically or closed with a transcatheter device. Patients do not need prophylaxis for endocarditis.

Key Definition

Ductus arteriosus: *normal embryologic structure connecting the descending thoracic aorta and the pulmonary artery.*

Eisenmenger Syndrome

Eisenmenger syndrome develops in the first few years of life when a large shunt (usually ventricular septal defect or patent ductus arteriosus or, less often, atrial septal defect) produces pulmonary hypertension as a result of irreversible pulmonary vascular disease. The increase of pulmonary pressure and right heart pressure promotes right-to-left shunting through the defect, leading to varying degrees of cyanosis. The condition is then inoperable, but with appropriate treatment, patients can survive decades; many series report median survival into the fifth decade. Heart failure, arrhythmias, hemoptysis, and stroke can all lead to death.

Cyanosis results in appropriate secondary erythrocytosis to increase oxygen delivery to the tissues. Routine phlebotomy is never indicated in Eisenmenger syndrome, and phlebotomy should not be performed on the basis of a hemoglobin value. Reduction in red cell mass decreases oxygen delivery to the periphery and results in symptoms of exercise intolerance. Repeated phlebotomy leads to iron deficiency, and because iron-deficient erythrocytes are more fragile, patients with iron deficiency have increased red cell destruction, which then increases blood viscosity and risk of stroke. Phlebotomy of any cyanotic patient should be performed only for symptoms of increased viscosity (eg, headache, altered mentation, long-bone pain), and decision about phlebotomy ideally should be guided by a specialist in adult congenital heart disease.

Fluid should be replaced concomitantly for patients with Eisenmenger syndrome. Hypotension and syncope may be fatal because of exacerbation of right-to-left shunting and hypoxia. Volume depletion, considerable exercise, and vasodilation should be avoided.

Pulmonary Stenosis

Pulmonary stenosis may occur as an isolated lesion or in association with other lesions.

Physical Examination

A delayed pulmonic valve component of the second heart sound may be heard; with severe stenosis, the pulmonic valve component becomes inaudible. The pulmonary opening click is the only right-sided sound that gets softer with inspiration as the pulmonary valve partially opens with the inspiratory increase in venous return. Later in life, the valve may become so thick, calcified, and immobile that the ejection click disappears. Findings of pulmonary stenosis include a prominent *a* wave in the jugular venous pulse (if the patient is in sinus rhythm) and an ejection systolic click.

Diagnosis

Electrocardiography shows right ventricular hypertrophy. Poststenotic pulmonary dilatation, especially of the left pulmonary artery (Figure 10.11), is the chest radiographic hallmark for pulmonary stenosis.

The diagnosis is reliably made with 2-dimensional echocardiography. Doppler echocardiography dependably predicts the gradient and estimates right ventricular pressure. For asymptomatic patients, treatment is indicated when the right ventricular systolic pressure approaches more than two-thirds the systemic blood pressure. The treatment of choice for a pliable noncalcified valve is percutaneous balloon valvuloplasty.

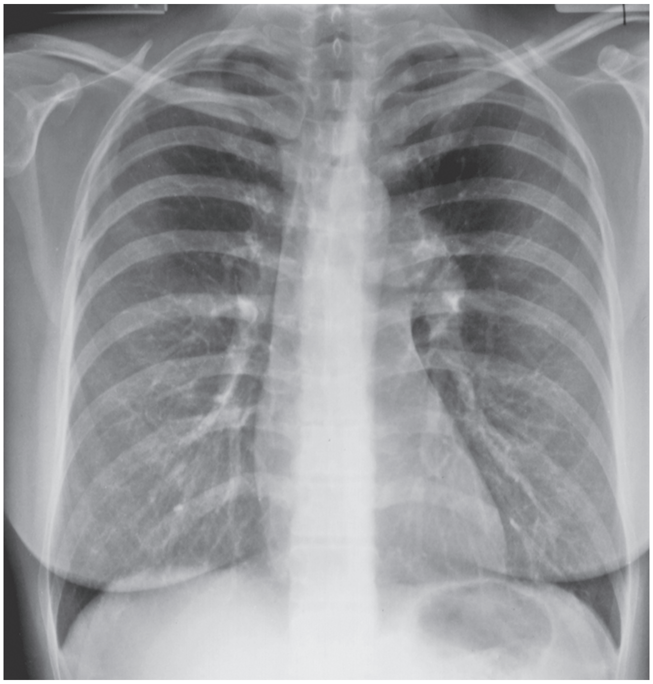


Figure 10.11. *Typical Chest Radiograph of a Patient With Valvular Pulmonary Stenosis. Normal cardiac size and marked prominence of main and left pulmonary arteries represent poststenotic dilatation. This does not occur with infundibular pulmonary stenosis. Lung fields appear mildly oligemic.*

Coarctation of the Aorta

This condition is usually either a discrete or a long segment of narrowing in the distal aortic arch. It is more common in boys and men than girls and women and frequently is associated with a BAV. Only about 20% of cases are diagnosed in adulthood.

Coarctation of the aorta is the most common cardiac anomaly associated with Turner syndrome. Other associations include aneurysms of the circle of Willis and aortic dissection or rupture. Prevalence of aortic dissection or rupture is increased in Turner syndrome, even in the absence of coarctation. If the coarctation is severe, systemic collateral vessels develop from the subclavian and axillary arteries through the internal mammary, scapular, and intercostal arteries. They may be identified by rib notching apparent on the chest radiograph.

Complications of coarctation are related to hypertension and abnormal arterial media and include stroke, aortic dilatation and dissection, intracranial artery aneurysm and dissection, premature coronary artery disease, and complications related to bicuspid aortic valve. Systemic hypertension may be the presenting clinical finding in adults younger than 50 years. Some patients report pain and fatigue in the legs on exercise, reminiscent of claudication.

Symptoms

Coarctation should be considered in patients with hypertension who are younger than 50 years. Coexistent lower-extremity claudication may exist. Patients may present with symptoms of aortic rupture, dissection, congestive heart failure, or associated conditions of Turner syndrome, circle of Willis aneurysm, or BAV.

Physical Examination

Findings include an easily palpable brachial pulse, but the femoral pulse is weak and delayed. Systolic pressure differences are detected between the upper and the lower extremities, and upper-extremity hypertension and lower-extremity hypotension are possible. Exercise may exaggerate systemic hypertension. An ejection click is present when there is an associated bicuspid valve. The aortic valve component may be loud as a result of hypertension. A fourth heart sound may be present with associated LV hypertrophy and hypertension. Murmurs may originate from 3 main developments. One is coarctation, which can produce a systolic murmur over the left sternal edge and over the spine in the midthoracic region. This sometimes extends into diastole in the form of a continuous murmur. Another is arterial collateral vessels that are spread widely over the thorax, and third is the bicuspid aortic valve, which may generate a systolic murmur.

Diagnosis

The electrocardiogram may be normal. LV hypertrophy with or without repolarization changes is more likely when coarctation stenosis and hypertension are more severe. Chest radiography may show rib notching from the dilated and pulsatile intercostal arteries and a “3” configuration of the aortic knob due to the coarctation site.

Treatment

Surgical treatment or percutaneous stent implantation may be used to manage coarctation. Even after repair, the hypertension rate is considerable. Up to 75% of treated patients with coarctation are hypertensive at 30-year follow-up after treatment. Patients surgically or percutaneously treated and with relief of aortic obstruction still need lifelong follow-up because they continue to be at risk for cardiovascular complications.

Ebstein Anomaly

Ebstein anomaly is a defect involving the tricuspid valve and the right ventricular myocardium. It is a congenital anomaly that forms when the tricuspid valve does not delaminate properly from the underlying myocardium, resulting in abnormally formed and displaced valve leaflets. The abnormal tricuspid valve is associated with varying degrees of regurgitation, but the regurgitation is often severe. The right ventricular myocardium is also abnormal in this condition. Approximately 50% of patients with Ebstein anomaly have an atrial septal defect. Accessory electrical conduction pathways that can lead to supraventricular tachycardia are also common. This anomaly has been associated with maternal lithium ingestion during pregnancy.

Symptoms

Patients with Ebstein anomaly may present with exercise intolerance, atrial arrhythmias, cyanosis (if an atrial septal defect is present), or symptoms of right heart failure.

Physical Examination

A prominent *v* wave may be present. This finding is variable because the large right atrium may accommodate a large tricuspid regurgitant volume. A right ventricular lift is noted. A holosystolic murmur increases on inspiration at the left sternal edge from tricuspid regurgitation. One or more systolic clicks are noted.

Diagnosis

Chest radiography shows a narrow vascular pedicle with an enlarged globular silhouette and right atrial enlargement. The lung fields are normal or oligemic. Electrocardiographic findings include tall P waves (so-called Himalayan P waves) and right bundle branch block. Two-dimensional and Doppler echocardiography precisely delineates the anatomy. Cardiac magnetic resonance imaging can be useful to evaluate right ventricular size and function. Cardiac catheterization is unnecessary to make the diagnosis of Ebstein anomaly. Electrophysiologic study may be necessary to delineate a bypass tract.

Treatment

Surgical repair or replacement of the tricuspid valve is indicated to prevent right ventricular failure. Closure of an atrial septal defect, if present, should be performed at the time of valve surgery. Patients with accessory conduction pathways may benefit from catheter ablation techniques.

KEY FACTS

✓ Eisenmenger syndrome—

- develops in first few years of life when a large shunt (usually a ventricular septal defect or a patent ductus arteriosus and less often an atrial septal defect) produces pulmonary hypertension because of irreversible pulmonary vascular disease
- cyanosis results in appropriate secondary erythrocytosis to increase oxygen delivery to tissues
- routine phlebotomy is never indicated and should not be performed on the basis of a hemoglobin value

✓ Coarctation of the aorta—has 5 major complications: cardiac failure, aortic valve disease, aortic rupture or dissection, endarteritis, and rupture of an aneurysm of the circle of Willis

11 Vascular Disease

ROBERT D. MCBANE, MD

Disease of the Aorta

Aneurysmal Disease

Thoracic Aortic Aneurysm

Aneurysms of the ascending aorta are typically due to medial degeneration, whereas aneurysms of the descending thoracic aorta are primarily due to atherosclerosis. Men and women are equally affected, and the prevalence of thoracic aortic aneurysm (TAA) increases with advancing age. Overall, the incidence is approximately 1 per 10,000 individuals, and 20% of patients with TAA have at least 1 affected first-degree relative. Typical risk factors include tobacco exposure, hypertension, infection, and trauma.

Temporal arteritis (age >50 years), Takayasu arteritis (age <50 years), Behçet disease, ankylosing spondylitis, and syphilis are relevant although uncommon acquired inflammatory causes to consider. Inherited mechanisms of disease fall into 2 categories, syndrome and nonsyndromic presentations. The syndromic conditions—Marfan, Loeys-Dietz, and Ehlers-Danlos syndromes—should be considered in young patients (age <40 years) with ascending aortic involvement (especially the root) and in patients with a family history of aortic dissection or sudden death. Specific clinical clues may include ectopia lentis (Marfan syndrome); bifid uvula; strong family history of aneurysms with rupture (Loeys-Dietz syndrome); visceral perforation such as gastrointestinal tract, uterine, or pneumothorax (Ehlers-Danlos syndrome); and webbed neck and short stature (Turner syndrome). A midsystolic click noted on cardiac auscultation should prompt echocardiographic evaluation for bicuspid aortic valve disease, which can have an associated aortopathy. Nonsyndromic presentations, termed *familial thoracic aortic aneurysms and dissection*, also should be considered in young patients with appropriate family history of aneurysmal disease.

Early-onset hypertension, intermittent claudication in young patients, or delay from the radial or brachial pulse to the femoral pulse should bring to mind coarctation. Up to 50% of patients with coarctation also will have bicuspid aortic valve. The converse is not true, however; only 6% of patients with bicuspid aortic valve disease will have coarctation. Intracranial aneurysms are common, occurring in 10% of patients with coarctation. Coarctation is prominent in Turner syndrome.

Most TAAs are asymptomatic and incidentally discovered on chest imaging (Figure 11.1). If they are symptomatic, patients may report chest or back pain, vocal hoarseness, cough, dyspnea, stridor, or dysphagia. Hemoptysis or hematemesis may occur in the clinical setting of erosion into adjacent structures. Findings on physical examination may include hypertension or fixed distention of a neck vein(s). Findings on cardiac examination may include midsystolic clicks (bicuspid aortic valve) and systolic or diastolic murmurs (aortic regurgitation). Other examination findings may include a fixed vocal cord, signs of cerebral or systemic embolism, or other aneurysmal disease (ie, abdominal aortic aneurysm [AAA]). It is important to search for synchronous aneurysms (ie, AAA, femoral and popliteal aneurysms), which can be present in 25% of patients. The diagnosis is confirmed with magnetic resonance imaging (MRI) (Figure 11.2A), computed tomography (CT) (Figure 11.2B), or transesophageal echocardiography (TEE).

Complications of TAA include rupture, dissection, or, rarely, thromboembolism. A direct correlation exists between aneurysm size and risk of rupture (diameter <4.0 cm, 0%; 4.0-5.9 cm, 16%; ≥6.0 cm, 31%). Hypertension, large aneurysm size, traumatic aneurysm, and associated coronary and carotid artery disease worsen the prognosis.

Hypertension treatment should include β-blockers or angiotensin receptor blockers. β-Blockers in patients with Marfan syndrome have been shown to slow aortic enlargement and may improve survival. Angiotensin receptor blockers are preferred for patients with Loeys-Dietz syndrome. These drugs also are reasonable for patients with TAA and no defined connective tissue

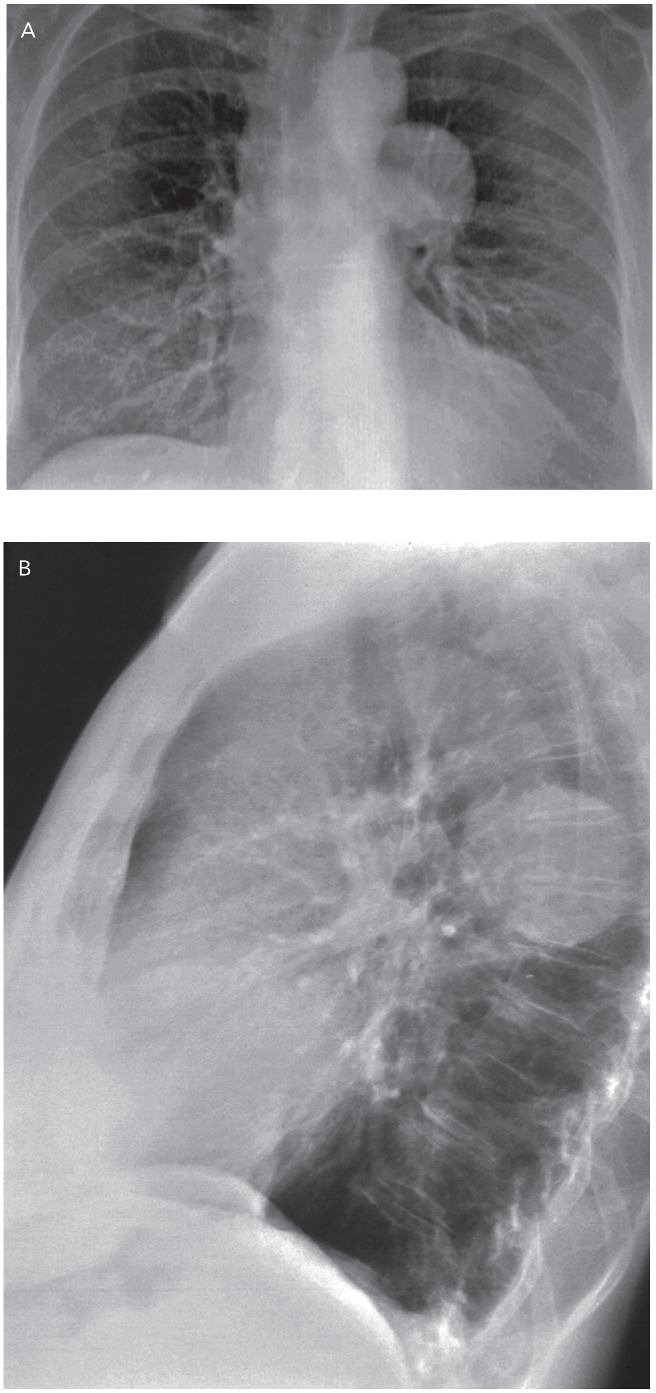


Figure 11.1. *Chest Radiographs for a Patient With Thoracic Aortic Aneurysm Showing a Large Mass in Left Posterior Aspect of Chest. A, Anteroposterior. B, Lateral.*

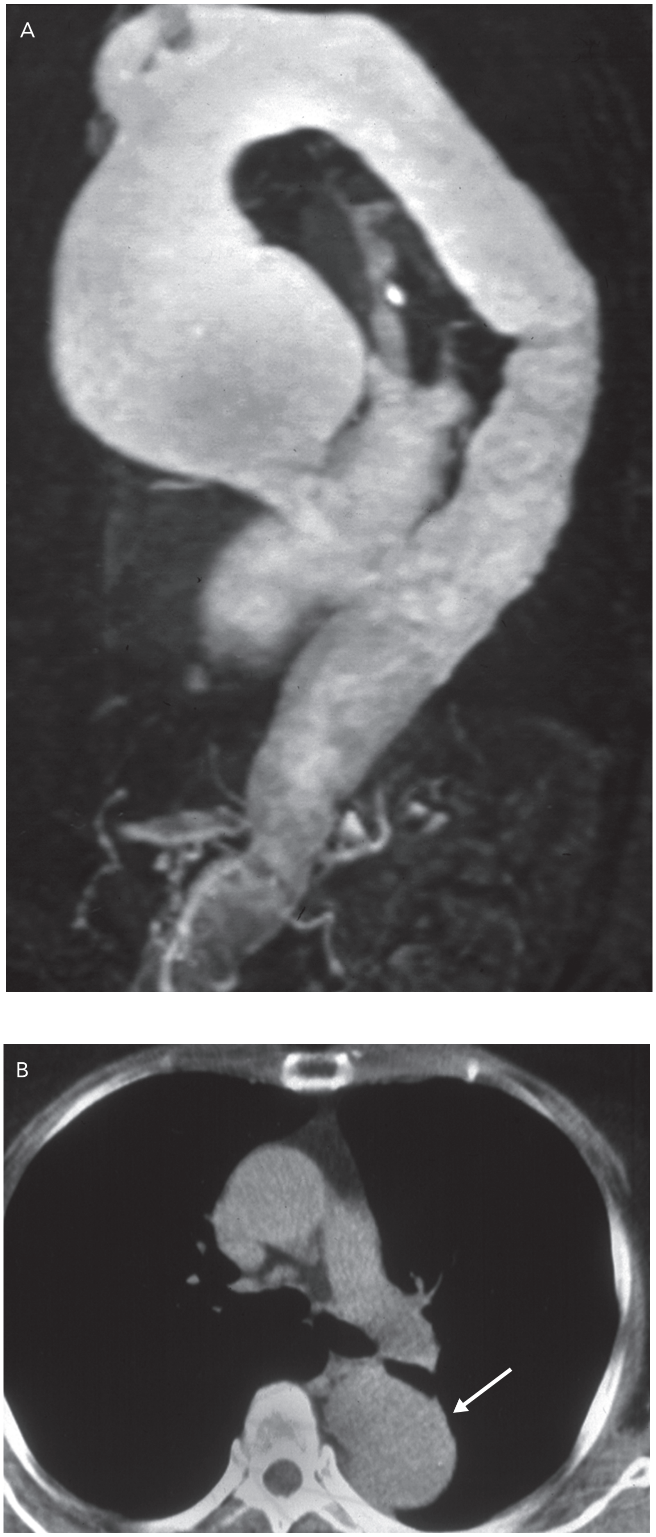


Figure 11.2. *Imaging of Thoracic Aortic Aneurysm. A, Magnetic resonance angiogram (longitudinal view) shows a large ascending aortic aneurysm and moderate aortic regurgitation. B, Computed tomogram shows a saccular aneurysm in the mid descending thoracic aorta (arrow).*

disease. Statin therapy to achieve a target low-density lipoprotein cholesterol value of 70 mg/dL or less is warranted (class IIa). Smoking cessation is always warranted.

Elective surgical repair is indicated for patients with degenerative TAA exceeding 5.5 cm or growth rate exceeding 0.5 cm per year. For patients with Marfan syndrome, the size criterion is 5.0 cm. Because Loeys-Dietz syndrome carries such a high risk of rupture, the size limit is 4.5 cm. For patients with bicuspid aortic valves, surgery is indicated if the aortic root or ascending aorta exceeds 5.5 cm or if growth rate exceeds 0.5 cm per year. For patients with inherited causes, TAA, and additional risk factors such as a family history of dissection, the size criteria for repair is adjusted downward by 0.5 cm.

Abdominal Aortic Aneurysm

The abdominal aorta is the most common site of aneurysm. Men are affected 5 times more often than women, and the incidence increases with age. The prevalence of AAA is 12% among men and 6% among women older than 65 years. Most aneurysms are small (<3.5 cm) and most are due to atherosclerosis. Tobacco use is a major risk factor. However, other diseases must be considered, including connective tissue diseases (Marfan syndrome, Ehlers-Danlos syndrome, and pseudoxanthoma elasticum), infection, trauma, or vasculitis (Takayasu arteritis and temporal arteritis). Of patients with AAA, 25% have an affected relative; thus, a familial predisposition is suspected. Most AAAs are infrarenal. Juxtarenal and suprarenal AAAs (2%-5%) are less common but are important to identify when considering management.

Most patients with AAA are asymptomatic. Livedo reticularis, painful blue toes with palpable pulses, hypertension, renal insufficiency, increased erythrocyte sedimentation rate, and transient eosinophilia imply AAA-associated atheroembolism (Figure 11.3). A history of new or worsening abdominal or low back pain suggests aneurysm instability. The triad of severe abdominal pain, hypotension, and a tender abdominal mass characterize AAA rupture. The annual risk of rupture is directly related to aneurysm size: 4.0 cm, <2%; 5.0 cm, 5%; 6.0 cm, 10%; and 7.0 cm or more, 20%.

The most common physical finding is a pulsatile abdominal mass; however, this finding lacks sensitivity, particularly for smaller aneurysms. A 1-time screening ultrasonography for men age 65 to 75 years who have ever smoked is recommended, and AAA screening is indicated for men age 60 years or older

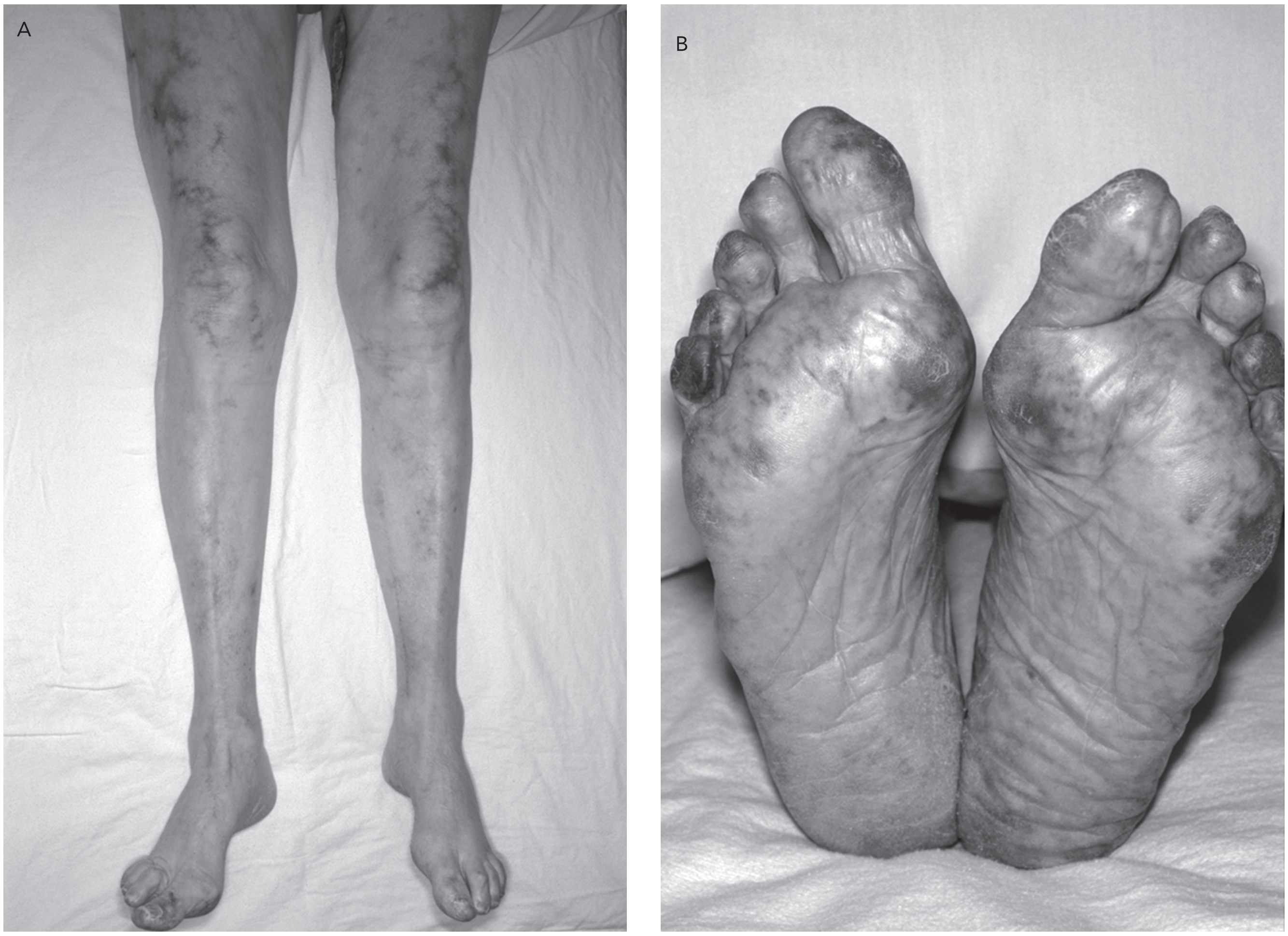


Figure 11.3. *Findings of a Patient With Atheroembolism. A and B, Livedo reticularis (upper aspect of thighs, plantar surface of feet) and multiple blue toes.*

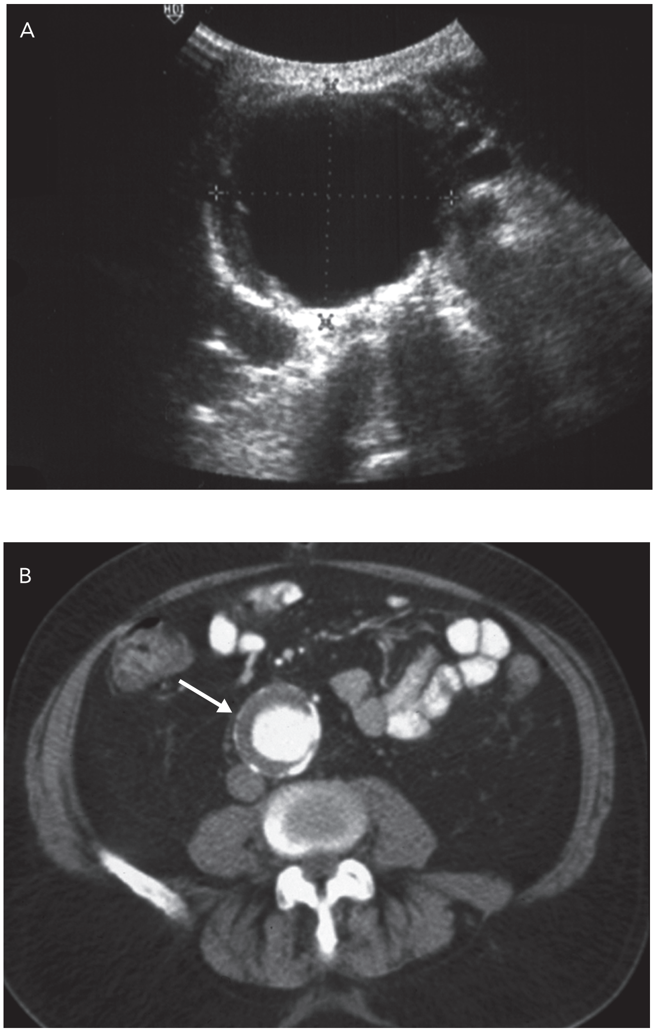


Figure 11.4. Imaging of Abdominal Aortic Aneurysm. A, Ultrasonogram (transverse view) shows a 4.7-cm aneurysm. B, Computed tomogram (contrast medium–enhanced) shows aneurysm (arrow).

who have a first-degree family history of AAA. Screening strategies for women are less clear and societal guidelines differ. It is reasonable to consider a 1-time screening ultrasonography for women older than age 65 years who have a history of smoking. Ultrasonography (Figure 11.4A), CT, and CT angiography (Figure 11.4B) or MRI and magnetic resonance (MR) angiography are reliable for diagnosis. AAA rupture accounts for more than 15,000 deaths annually in the United States. Only 20% of ruptures occur in patients with known AAA, a fact that underscores the importance of screening programs.

Medical management includes modification of atherosclerotic risk factors, including blood pressure control (preferably with a β-blocker), tobacco cessation, and statin therapy. If the aneurysm size is 4.0 cm or more, serial ultrasonography should be done every 6 to 12 months. For aneurysms less than 4.0 cm, imaging intervals can be extended to every 2 to 3 years. Repair is recommended for aneurysms of 5.5 cm or more, growth rate of 0.5 cm or more per year, atheroembolism, or any suggestion of instability.

Several trials have compared open to endograft repair of AAAs. The early outcomes (0 to 6 months) favor endovascular repair, including death, myocardial infarction, pneumonia, renal failure, and length of hospital stay. As such, most (>80%) patients with AAAs are now treated with endovascular repair with stent grafts. There appears to be a late catchup of mortality outcomes, which in part relates to endograft-associated complications.

Graft-related complication rates are higher for endovascular AAA repair. An endoleak (ie, persistent flow into the aneurysm sac, most often due to patent branch vessels feeding the aneurysm sac) is the most common graft-related complication. It usually is repaired with catheter-based techniques. Because of the risk of endovascular leak, serial surveillance is required indefinitely. For this reason, endovascular repair is often reserved for older patients with increased surgical risk, whereas open repair is recommended for younger patients at low to average surgical risk.

Thoracic Aortic Dissection

Acute thoracic aortic syndromes include aortic dissection (80%), intramural hematoma (10%), and penetrating aortic ulcer (10%). Aortic dissection begins with a tear through the arterial intima that allows pulsating blood to penetrate along the media longitudinally, separating the arterial wall. The dissection extends before either reentering the lumen through a second intimal tear or exiting the artery through an adventitial tear. Dissection can be catastrophic, including organ infarction or frank rupture. Causes include atherosclerosis, hypertension, cystic medial necrosis (ascending aorta, including connective tissue disease processes such as Marfan syndrome), bicuspid aortic valve disease, or trauma (blunt or penetrating). Dissection also may be iatrogenic (cardiac surgery, invasive angiography, or intra-aortic balloon pump). Aortic dissection may complicate pregnancy in at-risk women; when this occurs, it is usually in the third trimester.

An intramural hematoma occurs when bleeding develops within the media without a demonstrable intimal tear or flowing blood within a false lumen. A penetrating aortic ulcer results from ulceration that penetrates through the internal elastic lamina with bleeding into the media, often in a segment of atheromatous plaque. These clinical situations are treated in the same manner as dissections and depend on where the injury occurs (ascending vs descending thoracic aorta). Incomplete rupture of the thoracic aorta (in the region of the aortic isthmus) results from a sudden deceleration injury, frequently a motor vehicle crash (Figure 11.5).

Symptoms of aortic dissection include sudden-onset, severe, often migratory pain in the anterior aspect of the chest, back, or abdomen; these occur in 70% to 80% of patients (sensitivity of 90% and specificity of 84%). The pain is often described

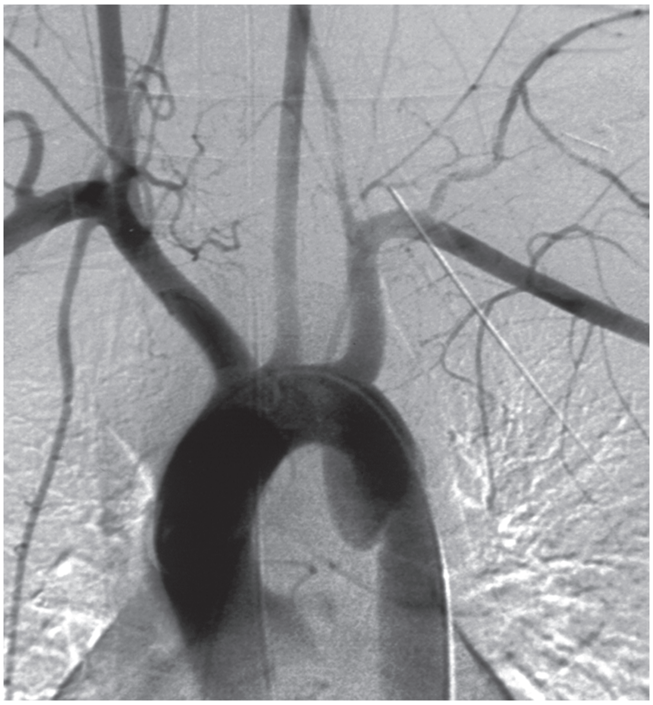


Figure 11.5. *Aortogram of Contained Rupture of Proximal Descending Thoracic Aorta Immediately Distal to Origin of Left Subclavian Artery. Patient was involved in a severe motor vehicle crash.*

as *ripping*, *tearing*, or *stabbing*. Hypertension is present in 70% of patients. For patients who have an ascending thoracic aortic dissection, additional signs may include a diastolic murmur due to aortic regurgitation (from disruption of the aortic annulus; 20%), pulse deficits (30%), neurologic changes (20%), and syncope (13%). A pulse deficit portends a worse outcome; in-hospital mortality rates are 45% (compared with 15% when pulses are present). Focal neurologic deficits imply carotid transection. Hypotension, tachycardia, jugular venous distention, systemic vascular congestion, and pulsus paradoxus suggest pericardial tamponade due to rupture into the pericardium. Congestive heart failure is usually due to acute, severe aortic regurgitation. Acute myocardial infarction, pericarditis, and complete heart block may also occur.

Chest radiography may show widening of the superior mediastinum (Figure 11.6), deviation of the trachea from the midline, a discrepancy in diameter between the ascending aorta and the descending aorta, and pleural effusion. Electrocardiography most commonly shows left ventricular hypertrophy, but ST-segment depression, ST-segment elevation, T-wave changes, and the changes of acute pericarditis and complete heart block occur in up to 55% of patients. Diagnosis is readily and accurately confirmed with TEE, CT angiography, and MR angiography (Figure 11.7). Test choice is determined by availability and local expertise.

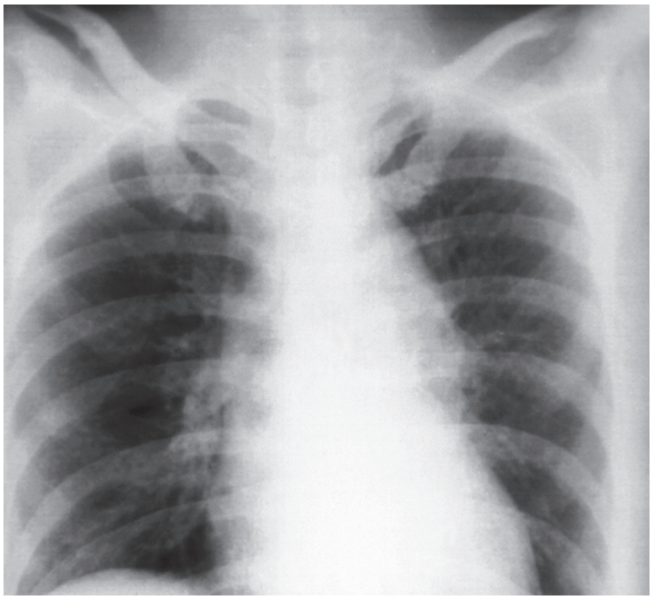


Figure 11.6. *Chest Radiograph of Aortic Dissection. Superior mediastinum is widened.*

Aortic dissections are classified by location relative to the ascending aorta and aortic arch (Figure 11.8). The 2 commonly used classification systems are DeBakey and Stanford. Aortic dissection involving the ascending aorta is designated as DeBakey type I or II (proximal, Stanford type A). Descending aortic dissection begins distal to the left subclavian artery orifice and is designated as DeBakey type III (distal, Stanford type B). Clinical clues to DeBakey type I and type II (ascending) aortic dissection include substernal pain, aortic valve incompetence, decreased pulse or blood pressure in the right arm, decreased right carotid pulse, pericardial friction rub, syncope, and ischemic electrocardiographic changes. Clinical clues to descending thoracic aortic dissection include interscapular pain, hypertension, and left pleural effusion.

Acute dissections of the ascending thoracic aorta are surgical emergencies because of mortality rates exceeding 1% per hour within the first 48 hours for untreated patients. In contrast, acute dissections of the descending thoracic aorta are typically managed medically with aggressive control of blood pressure and heart rate. Intravenous β-blockers (goal heart rate, <70 beats per minute) are indicated in the acute setting. Pharmacologic therapy should be instituted as soon as the diagnosis of any aortic dissection is suspected (Box 11.1). If systolic blood pressure stays greater than 120 mm Hg, angiotensin-converting enzyme inhibitors or other vasodilators should be administered. Indications for surgical repair for a descending thoracic aortic dissection include organ malperfusion, progression of the dissection despite aggressive heart rate and blood pressure control, aneurysm enlargement, and inability to control blood pressure

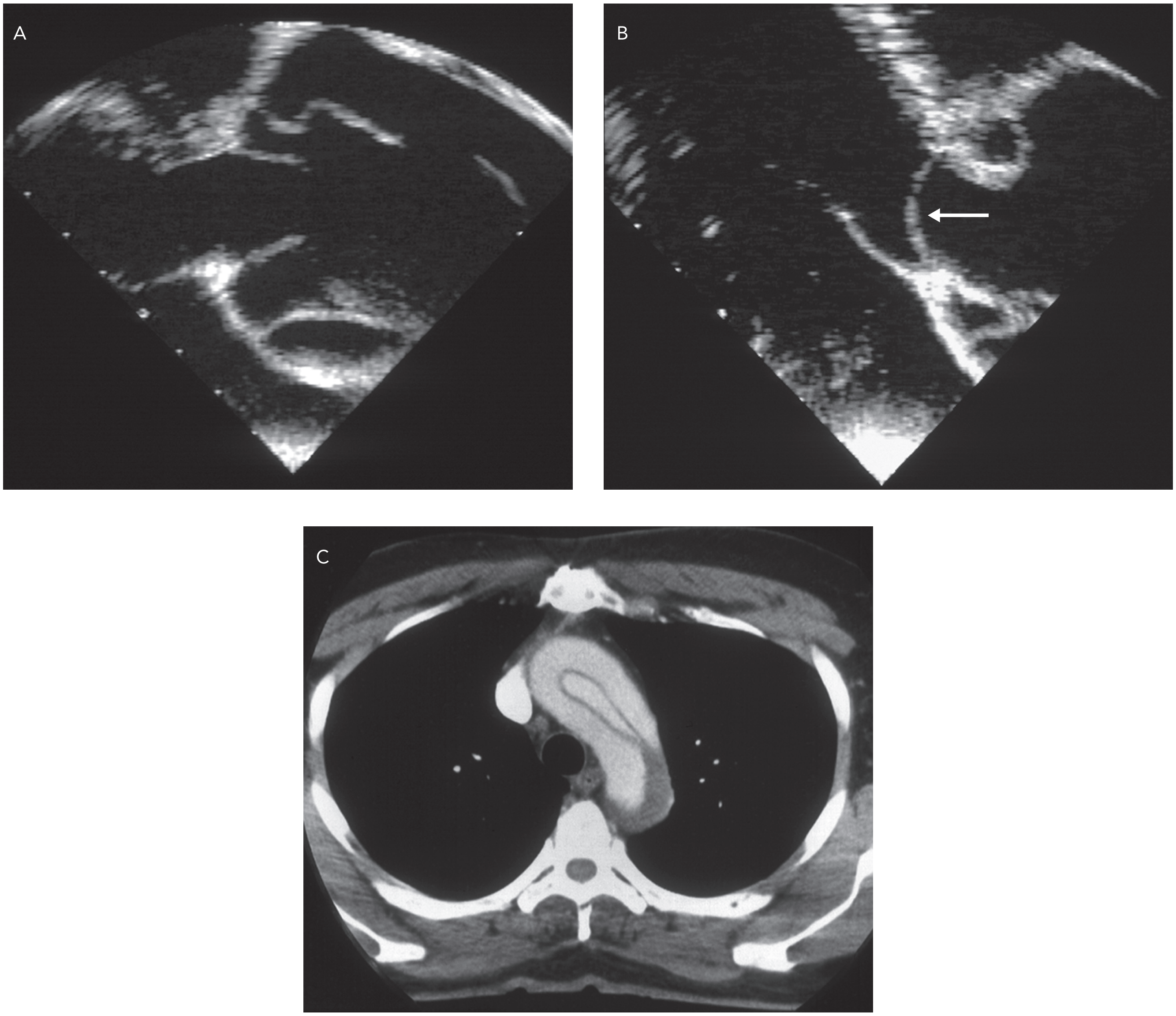


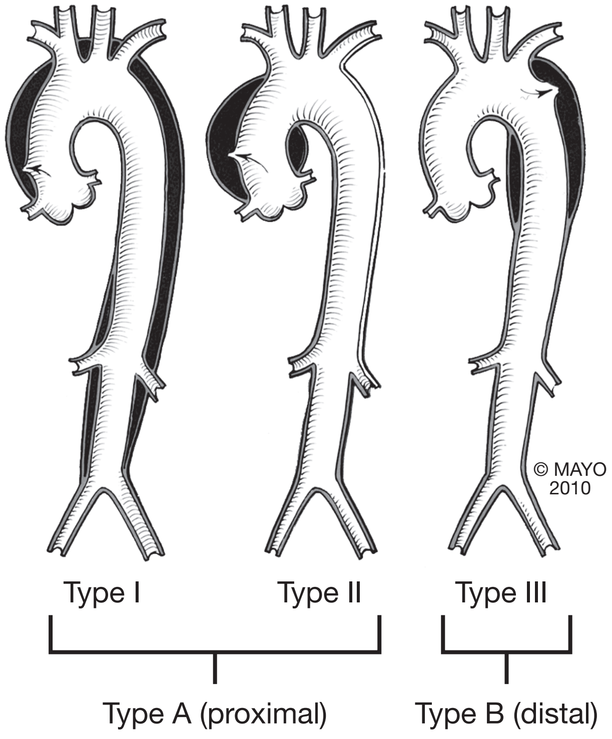
Figure 11.7. *Imaging of Aortic Dissection. A and B, Multiplane transesophageal echocardiograms. Longitudinal view (A) shows an intimal flap in the ascending aorta. In diastole (B), the intimal flap prolapses through the aortic valve (arrow). C, Computed tomogram (contrast medium–enhanced) shows a spiraling intimal flap in the transverse aortic arch.*

or symptoms of the dissection. There is now a growing trend to consider aortic stent grafts for descending thoracic aortic dissections to limit aortic injury, promote occlusion of the false lumen, and prevent late aortic ruptures.

Factors predicting a poor prognosis for descending thoracic aortic dissections and the need for surgical repair include aortic diameter more than 4.0 cm or a persistently patent false lumen. Preoperative coronary angiography in acute ascending aortic dissection is *not* indicated because of an association with an increased mortality rate. Treatment of an intramural hematoma or penetrating aortic ulcer is similar to treatment of dissection of the corresponding thoracic aortic segment (surgical if ascending and medical if descending). After the patient's vital signs are stabilized, serial imaging is necessary to monitor progression and development of aneurysmal disease. The management of acute aortic dissection is summarized in Figure 11.9.

KEY FACTS

- ✓ Aneurysms of ascending aorta—typically due to medial degeneration
- ✓ Aneurysms of descending thoracic aorta—primarily due to atherosclerosis
- ✓ Indications for elective surgical repair of TAA—ascending TAA ≥5.5 cm, descending TAA ≥6.0 cm, or growth rate ≥0.5 cm per year
- ✓ AAA—
  - men are affected 5 times more often than women, and incidence increases with age
  - ≥4.0 cm: ultrasonography every 6-12 months
  - <4.0 cm: ultrasonography every 2-3 years
  - repair recommended for size ≥5.5 cm, growth rate ≥0.5 cm per year, atheroembolism, any suggestion of instability
- ✓ All ascending thoracic aortic dissections (Stanford type A or DeBakey type I or II)—surgical emergencies (mortality rate is 1% per hour within the first 48 hours if left untreated)
- ✓ Descending thoracic aortic dissection (Stanford type B or DeBakey type III)—treated medically unless there is organ ischemia, dissection progression, enlarging aneurysm, or inability to control pain or hypertension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Type I
Type II
Type III
Type A (proximal)
Type B (distal)

Figure 11.8. *Classification Systems for Aortic Dissection.*

Box 11.1 • Initial Pharmacologic Therapy for Acute Aortic Dissection

Hypertensive patients

Sodium nitroprusside intravenously (2.5-5.0 mcg/kg/min)

with

Propranolol intravenously (1 mg every 4-6 h)

Goal: systolic blood pressure in the range of 110 mm Hg (or the lowest level maintaining a urine output of 25-30 mL/h) until oral medication is started

or

Esmolol, metoprolol, or atenolol intravenously (in place of propranolol)

or

Labetolol intravenously (in place of sodium nitroprusside and a β-blocker)

Normotensive patients

Propranolol intravenously (1 mg every 4-6 h) or orally (20-40 mg every 6 h) (metoprolol, atenolol, esmolol, or labetalol may be used in place of propranolol)

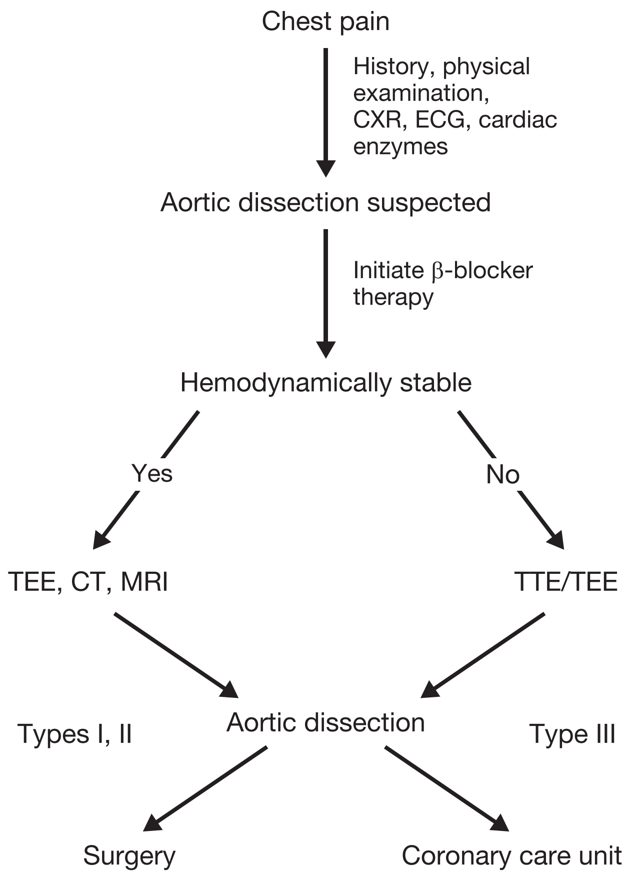

Chest pain
History, physical examination, CXR, ECG, cardiac enzymes
Aortic dissection suspected
Initiate β-blocker therapy
Hemodynamically stable
Yes
No
TEE, CT, MRI
TTE/TEE
Aortic dissection
Types I, II
Type III
Surgery
Coronary care unit

Figure 11.9. *Algorithm for Initial Management of Suspected Acute Aortic Dissection. CT indicates computed tomography; CXR, chest radiography; ECG, electrocardiography; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.*

Peripheral Arterial Conditions

Aneurysms

Iliac artery aneurysms are usually associated with AAA, but they may occur as an isolated finding. Symptoms at presentation may include urinary obstruction, iliac vein obstruction, and unexplained groin or perineal pain. Repair is indicated when the aneurysm size exceeds 3.5 cm. Femoral artery aneurysm repair is indicated at a size of 3.0 cm or more. Popliteal artery aneurysm may lead to thromboembolization, neuropathy, or thrombophlebitis. Repair is indicated when the aneurysm is more than 2 cm or when thrombus is present. The greatest concern for popliteal aneurysm is thromboembolism to distal arteries. Popliteal artery aneurysm is bilateral in 50% of patients, and 40% of patients may have synchronous aneurysms elsewhere, most commonly the abdominal aorta.

Arterial Occlusive Disease

Peripheral artery disease (PAD) of the legs may be symptomatic at presentation (50%) or may be found incidentally (50%). Of symptomatic patients, 40% have intermittent claudication and 10% have critical limb ischemia at diagnosis. **Intermittent claudication** is the most common symptom and is defined as "exertional pain involving the calf that impedes walking, resolves within 10 minutes of rest, and neither begins at rest nor resolves on walking" (Monogr Ser World Health Organ. 1968;56:1-188). Pseudoclaudication (due to lumbar spinal stenosis) is the condition most commonly confused with intermittent claudication. Clinical clues suggesting pseudoclaudication include day-to-day variability of distance to symptom onset, symptom onset with prolonged standing (spinal extension), and need to sit for symptom relief (spinal flexion) (Table 11.1). Other clues may include a history of back pain or prior spinal operations. Lumbar spinal stenosis can be confirmed with a normal or minimally abnormal ankle-to-brachial systolic pressure index (ABI) before and after exercise, in combination with characteristic findings on electromyography and CT or MRI of the lumbar spine.

Symptoms of walking impairment for patients with PAD are stable in 75% of affected patients, and less than 2% per year require amputation. However, mortality rate is high (5 years, 30%; 10 years, 50%; 15 years, 70%), reflecting coexisting atherosclerosis: severe coronary artery disease (40%-60%), carotid artery disease (25%-50%), and renal artery disease (25%-40%).

Key Definition

Intermittent claudication: *exertional pain involving the calf that impedes walking, resolves within 10 minutes of rest, and neither begins at rest nor resolves on walking.*

Table 11.1 • Differential Diagnosis of Intermittent Claudication and Pseudoclaudication

Factor	Claudication	Pseudoclaudication
Onset	Walking	Standing and walking
Character	Cramp, ache	Paresthetic
Bilateral	Sometimes	Often
Walking distance	Fairly constant	More variable
Cause	Atherosclerosis	Spinal stenosis
Relief	Standing still	Sitting down, leaning forward

ABI screening should be performed for patients with exertional leg symptoms, patients 50 to 60 years old with atherosclerosis risk factors (especially diabetes mellitus or smoking), patients older than 70 years, or patients with a Framingham risk score of more than 10%. Disease severity assessed by ABI criteria correlate directly with overall survival such that the severity of PAD is an independent predictor of all-cause mortality. Patients with diabetes mellitus should be screened every 5 years. Supine ABIs before and after exercise testing (treadmill walking or active pedal plantar flexion) confirm the diagnosis (Table 11.2). An ABI index between 1.0 and 1.4 is considered normal. Values of 0.5 or less are considered severely reduced. If ABIs are normal at rest but symptoms are suggestive of intermittent claudication, ABIs should be determined before and after treadmill exercise. Calcified peripheral arteries may result in a falsely increased Doppler-derived systolic pressure and invalidate the ABI (≥1.4). In these cases, an accurate pressure may be obtained by measuring the toe pressure and calculating the toe-brachial index (a pressure gradient of 20-30 mm Hg is normally present between the ankle and the toe). An abnormally high ABI (≥1.4) implies arterial calcification and is associated with diabetes and with increased cardiovascular risk.

Table 11.2 • Grading System for Lower-Extremity Arterial Occlusive Disease

	ABI	
Grade	**Supine Resting**	**Postexercise**[a]
Normal	1.0-1.4	≥1.0
Minimal disease	0.9-1.0	0.8-1.0
Mild disease	0.8-0.9	0.5-0.8
Moderate disease	0.5-0.8	0.15-0.5
Severe disease	<0.5	<0.15

Abbreviation: ABI, ankle-to-brachial systolic pressure index.

[a] After treadmill exercise (1-2 mph, 10% grade for 5 minutes or until limited by symptoms) or active pedal plantar flexion (50 repetitions or until limited by symptoms).

Smoking cessation and treatment to lower lipid levels and to control diabetes mellitus and hypertension according to national treatment guidelines are recommended for all patients with PAD. For patients who continue to use tobacco, the risk of major amputation is increased 10-fold and the mortality rate is increased more than 2-fold. Diabetes mellitus accounts for most amputations (12-fold increased risk of below-knee amputation).

All patients with PAD should receive aspirin (81-325 mg daily) or have clopidogrel if they are allergic to aspirin. Clopidogrel (75 mg daily) has been shown to be more effective than aspirin for preventing major atherosclerotic vascular events in patients with PAD. Cilostazol can be used for relief of claudication symptoms and improves walking distance to claudication compared with pentoxifylline or placebo, but it is *contraindicated* in patients with heart failure. Although there is no evidence that treatment of hypertension alters the progression of claudication, blood pressure should be controlled to reduce morbidity and death due to cardiovascular and cerebrovascular disease. The angiotensin-converting enzyme inhibitor ramipril reduces the risk of ischemic cardiovascular events in patients with PAD and may increase walking distance in selected patients, in addition to its renal protective effects in diabetes. Statins reduce cardiovascular events in patients with PAD, reduce new or worsening claudication, and improve walking distance and pain-free walking time. All patients with PAD should receive treatment to reduce the low-density lipoprotein cholesterol value to less than 100 mg/dL (<70 mg/dL in patients with atherosclerosis in other circulatory beds).

Systemic antibiotic therapy should be initiated promptly in patients with critical limb ischemia, skin ulcerations, and evidence of limb infection. Patients at risk for critical limb ischemia (ABI <0.4 in a nondiabetic patient or in any diabetic person with known lower-extremity PAD) should undergo regular foot inspection to detect objective signs of critical limb ischemia. Foot care and protection are of paramount importance for patients with diabetes mellitus who have PAD. The combination of peripheral neuropathy, small-vessel disease, and PAD in patients with diabetes mellitus makes foot trauma more likely to be associated with a nonhealing wound or ulcer.

Supervised walking should be part of the initial treatment for all patients with PAD. Maximal walking distance has been shown to improve 200% to 300% when treadmill or track walking is used to the point of symptom reproduction with rest intervals in 30- to 60-minute sessions, 3 times weekly for 3 months.

Absolute indications for revascularization (surgical bypass or angioplasty and stenting) include ischemic rest pain and nonhealing ulceration. Ischemic ulcers are typically found at pressure points on the foot (eg, between-toes “kissing ulcers”) and point of contact with a shoe (eg, medial aspect of great toe, lateral aspect of fifth toe, and heels). A relative indication for revascularization includes lifestyle-limiting intermittent claudication. MR angiography and CT angiography define the anatomic localization of disease and provide a roadmap necessary for endovascular or surgical therapeutic planning.

Indications for amputation are severe rest pain with no revascularization option, limb gangrene, or life-threatening infection. Below-knee amputation is associated with a mortality rate of 10% perioperatively and 25% at 1 year. The primary healing rate with below-knee amputation is 60%, and 15% of patients who have had below-knee amputation will eventually need above-knee amputation.

Acute Arterial Occlusion

Acute arterial occlusion is suggested by the sudden onset of extreme pain and paresthesia of the involved limb. These and other suggestive conditions are listed in Box 11.2. It is important to distinguish thrombus due to local plaque rupture from an embolic source because the natural histories of these 2 mechanisms differ. Features suggestive of local thrombus include known arterial occlusive disease of the involved limb, which can be identified by examining the pulse integrity of the opposite limb. Diminished or absent pulses in the unaffected limb suggest underlying atherosclerosis and plaque rupture with associated thrombosis as the most likely mechanism. An embolic cause is suggested by the presence of cardiac disease (valvular or ischemic), atrial fibrillation, proximal aneurysm, or proximal atherosclerotic disease.

Therapeutic results from thrombectomy are much better when the acute arterial occlusion is due to embolism as opposed to plaque rupture with local thrombus. Amputation rates are considerably higher for patients with local thrombus. Infrequent causes of arterial occlusion include dissection, traumatic transection, vasculitis, sepsis or disseminated intravascular coagulation, compartment syndrome, vasospasm, foreign body embolization, or tumor. Tissue tolerance to ischemia varies by tissue type. Nerve injury occurs within 4 hours, whereas muscle (6 hours) and skin (10 hours) are relatively more resistant to ischemia. Angiography is performed after initiation of intravenous heparin therapy and foot protection. After confirmation of the diagnosis, initial therapeutic options include intra-arterial thrombolysis and surgery (thromboembolectomy). If thrombolysis is the initial treatment, percutaneous treatment or surgical therapy is usually indicated for the underlying stenosis (if present) and for improvement of long-term patency rates.

Box 11.2 • The 6 P’s Suggestive of Acute Arterial Occlusion

Pain
Pallor
Paresthesia
Paralysis
Poikilothermy (coldness)
Pulselessness

Fluid resuscitation is needed to prevent reperfusion syndrome, including myoglobinuric renal failure, metabolic (lactic) acidosis, and hyperkalemia. Four-compartment fasciotomy is often required to prevent muscle and nerve injury associated with the compartment syndrome.

Carotid Artery Disease

Carotid artery disease is present in 5% to 9% of the US population older than 65 years and contributes substantially to transient ischemic attacks and strokes. Large-vessel disease, most commonly of the carotid artery, accounts for 30% of ischemic strokes. The mechanism of stroke in the setting of severe carotid disease is typically plaque rupture with embolization. Cardiac embolism (especially atrial fibrillation) and small-vessel disease each account for an additional 30%. Carotid disease may initially be detected as a bruit. The prevalence of an asymptomatic bruit may be as high as 13% depending on the population examined. The prevalence increases with age.

The natural history of carotid artery disease varies by the clinical presentation (whether symptomatic or asymptomatic) and the severity of the underlying stenosis. When the clinical presentation is consistent with either transient ischemic attack or stroke, it is important to distinguish anterior from posterior circulation and right from left hemispheric injury to determine whether the carotid lesion is responsible for the symptoms. Symptomatic carotid artery lesions typically result in cortical neurologic deficits, whereas small-vessel mechanisms involve the deep parenchyma. A serious stenosis is typically defined as more than 70%. For asymptomatic carotid artery stenosis of more than 70%, the annual risk of stroke is between 3% and 4%. If the stenosis is less than 60%, the annual risk of stroke is less than 1%. For symptomatic patients with stenoses greater than 70%, the annual risk of stroke is 15%.

Medical treatment of all patients with carotid artery disease should include aggressive treatment of hypertension, hyperlipidemia, and diabetes mellitus. Cessation of the use of all tobacco products is strongly recommended. Antiplatelet therapy should be initiated.

Carotid endarterectomy reduces the annual risk of stroke in asymptomatic and symptomatic patients. For asymptomatic patients, this annual risk can be reduced from 4% to 1.5%. For symptomatic patients, the annual stroke rate can be reduced from 15% to 5% and perhaps to as low as 1.6%, according to trial data. Risks associated with carotid surgery include stroke and cranial nerve injury. Compared with stenting, surgery is associated with a slightly higher risk of myocardial infarction but perhaps a slightly lower risk of stroke.

The risk of adverse outcomes (stroke, myocardial infarction, or death) with carotid artery stenting is similar to that of carotid artery surgery in asymptomatic patients with substantial carotid artery stenosis. For asymptomatic patients in the Carotid Revascularization Endarterectomy vs Stenting Trial, the risk of stroke or death was 4.5% with carotid stenting and 2.7% with surgery. For symptomatic patients in that trial, this combined outcome was 8.0% for stenting and 6.4% for surgery. According to the guidelines, both stenting and surgery are acceptable for symptomatic patients. In general, for symptomatic patients who are at medical optimization for a surgical procedure, carotid endarterectomy should be pursued. For high-risk symptomatic patients who would not be good candidates for surgery, carotid stenting with an embolic protection device should be considered. For asymptomatic patients, revascularization should be determined on the basis of comorbidities, life expectancy, and other factors, including a thorough discussion of risks and potential benefits (untreated annual stroke risk, 4% per year).

KEY FACTS

- ✓ PAD—risk of death correlates strongly with coexisting systemic cardiovascular disease
- ✓ Iliac artery aneurysm—repair is indicated when aneurysm size is >3.5 cm
- ✓ Femoral artery aneurysm—repair is indicated when aneurysm size is ≥3.0 cm
- ✓ ABI criteria—normal is 1.0-1.4; severe, <0.5
- ✓ Cilostazol—improves walking distance for patients with arterial occlusive disease but is contraindicated for patients with clinical heart failure
- ✓ Symptomatic carotid artery disease (>70% stenosis)—in low-risk patients, treatment is surgical endarterectomy; in high-risk patients, stenting is used for treatment
- ✓ Asymptomatic carotid artery disease (<70% stenosis)—treatment can be surgical, stenting, or medical (4% risk of stroke per year)

Uncommon Types of Arterial Occlusive Disease

Thromboangiitis Obliterans (Buerger Disease)

Thromboangiitis obliterans (Buerger disease) (Table 11.3) should be considered in young smokers with foot claudication or ulceration of the feet or hands (Figure 11.10). These patients have early symptom onset, typically in the second to fourth decade of life. Foot claudication is nearly universal, and hand or finger involvement occurs in 33% to 63% of patients. All 4 limbs are involved in 40% of patients. Rest pain and ischemic ulceration are typically present in the lower extremity. Thromboangiitis obliterans affects distal arteries initially and primarily. Venous involvement (superficial phlebitis)

Table 11.3 • Clinical Criteria for Thromboangiitis Obliterans

Age	<40 years (often <30 years)
Sex	Male most often
Habits	Use of tobacco, cannabis
History	Superficial phlebitis Claudication of arch or calf Secondary Raynaud phenomenon Absence of atherosclerotic risk factors other than smoking
Examination	Small arteries involved Upper extremity involved (positive Allen test) Infrapopliteal artery disease
Laboratory findings	Normal values of glucose, blood cell counts, erythrocyte sedimentation rate, lipids, and screening tests for connective tissue disease and hypercoagulable disorders
Radiography	No arterial calcification

is common. The disease was previously considered a male-dominated disease, but the incidence in women has increased in recent decades. A hallmark of the disease is addiction to tobacco. Smoking cessation ameliorates the course of the disease and reduces the risk of ulcer formation and amputation.

Evaluation must be thorough and must distinguish between thromboangiitis obliterans and premature atherosclerosis. Distinguishing features of thromboangiitis obliterans include upper-extremity involvement, foot claudication, and a history of superficial thrombophlebitis. Patients may present in their early 20s and 30s, whereas even profound premature atherosclerosis does not usually present until the fifth decade of life.

Angiographic features include normal proximal vessels, distal artery occlusions, and skip lesions. *Tree root, spider*, and *corkscrew* are adjectives frequently applied to the angiographic appearance of collateral vessels and vasa vasorum; however, these findings are nonspecific and may be present in occlusive disease of other causes. Involved vessels may be thrombosed. Thrombi are infiltrated with inflammatory cells, but inflammatory markers (ie, erythrocyte sedimentation rate) are nearly always normal.

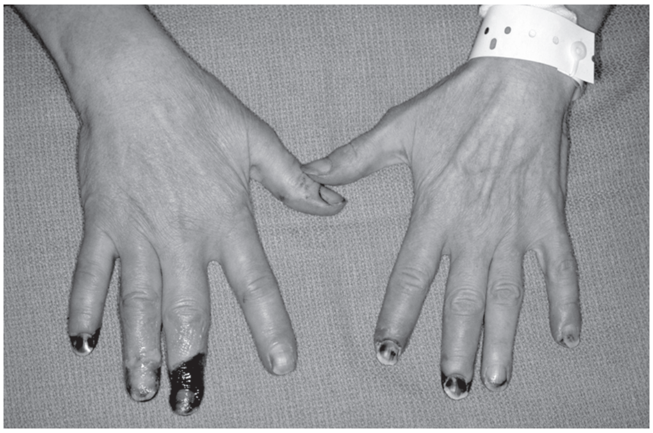


Figure 11.10. *Gangrene of the Tips of Multiple Upper-Extremity Digits in a Patient With Thromboangiitis Obliterans.*

Treatment is limited to tobacco cessation, wound care, limb protection, and amputation when needed. Arterial bypass grafting and angioplasty with stenting are rarely possible or effective.

Thoracic Outlet Compression Syndrome

The thoracic outlet syndromes are a group of often disabling disorders caused by mechanical compression or irritation of the neurovascular bundle as it leaves the chest cavity through the thoracic outlet. The syndromes have 3 unique clinical presentations: neurogenic, venous, and arterial. The thoracic outlet boundaries consist of the superior surface of the first rib and the anterior and middle scalene muscles. The neurogenic type is the most common (80% of patients) and presents with numbness, pain, and tingling primarily involving the ulnar nerve. Patients report arm symptoms with arm elevation (abduction), such as when working with their arms above their heads. The differential diagnosis of neurogenic thoracic outlet syndrome is broad and includes multiple neurologic, orthopedic, and vascular diagnoses. Electromyographic results are normal. Cervical spine radiographs may be helpful to show the presence of cervical rib arising from the C7 pedicle (as opposed to T1). Arm lowering (adduction) relieves symptoms. Approximately 15% of patients present with venous symptoms, including subclavian vein thrombosis (Paget-Schroetter syndrome or effort thrombosis). Approximately 5% of patients have an aneurysm of the subclavian artery as a result of trauma at the point where the artery crosses the outlet. Subclavian artery aneurysms tend to thrombose and embolize. Patients present with painful embolic digital artery occlusion and finger gangrene.

The diagnosis of neurogenic thoracic outlet syndrome is complex and is based primarily on clinical presentation and physical findings. Thoracic outlet maneuvers (costoclavicular active, costoclavicular passive, hyperabduction, Adson, and elevated arm stress tests) are performed to aid in the diagnosis. These maneuvers induce dynamic compression of the axillary-subclavian artery, which is identified as dynamic obliteration of the radial pulse. Results of these maneuvers may be positive in up to 30% of the general population; thus, their specificity and positive predictive value are limited. Vascular imaging (ultrasonography, CT angiography, and MR angiography) for neurogenic thoracic outlet syndrome shows dynamic vascular compression with maneuvers in up to 30% of the general population; thus, the usefulness of imaging in diagnostic evaluation is limited. Electromyography is normal in the majority of patients, such that an abnormal result should prompt a search for alternative diagnoses.

Treatment of neurogenic thoracic outlet syndrome is primarily and initially conservative with physical therapy. Severe cases in which conservative therapy fails may benefit from thoracic outlet decompression and first rib resection. Patients with upper-extremity venous thrombosis related to thoracic outlet syndrome (Paget-Schroetter syndrome or effort thrombosis) should receive aggressive thrombolytic therapy, anticoagulation, and first rib resection. Patients with upper-extremity arterial thrombosis related to thoracic outlet syndrome often present with digital ischemia related to thromboembolism from an axillary-subclavian artery aneurysm. These patients undergo aggressive treatment with surgical repair of the aneurysm, anticoagulation, and thoracic outlet decompression.

Vasospastic Disorders

Vasospastic disorders are characterized by episodic color changes of the skin resulting from intermittent spasm of the small arteries and arterioles of the skin and digits. These vascular disorders are important because they may be a clue to another, underlying disorder, such as arterial occlusive disease, connective tissue disorders, arterial injury, neurologic disorders, or endocrine disease. Vasospastic disorders may also be caused by certain medications, particularly β-blockers. Other possible causes are the use of ergot preparations, estrogen therapy, chemotherapeutic agents, interferon, cyclosporine, clonidine, narcotics, nicotine, and cocaine.

Raynaud Syndrome

For this syndrome, it is important to differentiate vasospasm due to primary Raynaud *disease* from secondary Raynaud *phenomenon* (due to a fixed obstruction) (Table 11.4). The natural histories of these 2 disorders differ considerably.

Primary Raynaud Disease

Raynaud disease typically involves the digits of the upper extremity and, to a lesser extent, the lower extremity. Women are more often affected than men, and the typical patient is less than 40 years old at onset of the disease. Vasospasm is induced by cold weather or emotional stress. Involvement is typically bilateral with multiple, if not all, digits involved. The symptoms are usually stable over time. Triphasic color changes (blanching, cyanosis, and hyperemic response to warming) may be present but are not universal. Other features of connective tissue disease such as systemic lupus erythematosus, rheumatoid arthritis, or scleroderma are absent. Arterial occlusion and digital ulcerations are rare. Raynaud disease is considered a benign condition, and treatment emphasizes avoiding cold exposure and vasoconstrictive triggers. Vasodilator therapy includes calcium channel blockers (dihydropyridine) and α-blockers (doxazosin).

Table 11.4 • Characteristic Clinical Features of Primary Raynaud Disease and Secondary Raynaud Phenomenon

Clinical Feature	Primary	Secondary
Symmetry	Bilateral	Unilateral or bilateral
Pulses	Normal	Abnormal
Skin ulcers	Absent	May be present
Gangrene, tissue loss	Absent	May be present
Vascular laboratory finding	Vasospasm	Fixed obstruction
Other underlying connective tissue disease	Absent	Present
Response to vasodilator or warming	Present	Minimal

Secondary Raynaud Phenomenon

In contrast to patients with Raynaud disease, those with secondary Raynaud phenomenon are more commonly male and older than 40 years. There is evidence of fixed digital artery obstruction, which may be due to various causes, including atherosclerosis, vasculitis, connective tissue diseases, hypothenar hammer syndrome, embolism, or drugs (especially β-blockers and ergotamine). Distribution of symptoms is asymmetrical with involvement of few digits. Associated pulse deficits, ischemic changes (including digital ulcerations), and systemic signs and symptoms are often present. Identification of the underlying cause is essential for appropriate treatment.

Evaluation should focus on differentiating primary Raynaud disease from secondary Raynaud phenomenon, including exclusion of connective tissue diseases and vasculitis. Vascular laboratory testing is important to differentiate vasospasm from arterial occlusion. Baseline laboratory tests include complete blood cell count, erythrocyte sedimentation rate, C-reactive protein, serum protein electrophoresis, antinuclear antibody, antiphospholipid antibody, and cryoglobulins. Conventional angiography (arch angiography with upper-extremity runoff) is rarely needed for the evaluation of primary Raynaud disease but can often be helpful for the evaluation of secondary Raynaud phenomenon, particularly when the underlying disease is not apparent.

Livedo Reticularis

Livedo reticularis is due to spasm or occlusion of dermal arterioles, leading to a bluish mottling of the skin in a lacy, reticular pattern (Figure 11.3). Primary livedo reticularis is idiopathic and not associated with an identifiable underlying disorder. Secondary livedo reticularis may result from atheroembolism from a proximal aneurysm or from proximal atheromatous plaques. Other causes of secondary livedo reticularis include connective tissue disease, antiphospholipid antibody syndrome, vasculitis, myeloproliferative disorders, dysproteinemias, reflex sympathetic dystrophy, cold injury, and an adverse effect of amantadine hydrochloride therapy.

Chronic Pernio

Chronic pernio is a vasospastic disorder characterized by sensitivity to cold and predominantly occurs in female patients

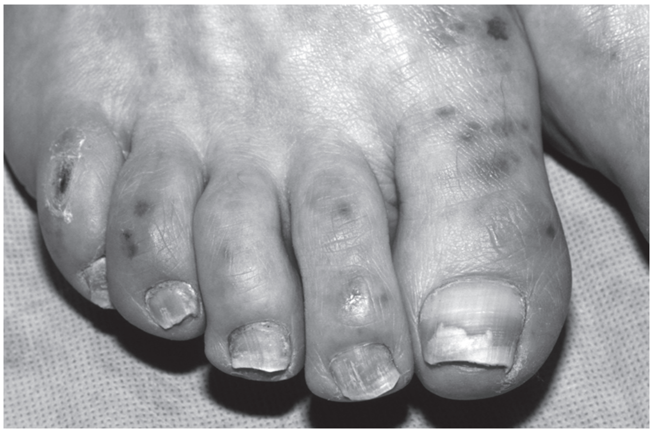


Figure 11.11. *Characteristic Lesions of Chronic Pernio.*

with a past history of often intense cold exposure and injury. It may result in a blistering process with ulceration, particularly of the toes (Figure 11.11). Chronic pernio typically presents with symmetrical blue discoloration and blistering and ulceration of the toes in cooler weather with resolution during warmer weather. Treatment with an α-blocker can be effective.

KEY FACTS

- ✓ Thromboangiitis obliterans (Buerger disease)—should be considered in young smokers with foot claudication or digital ulceration of feet or hands
- ✓ Thoracic outlet compression syndromes—the 3 unique clinical presentations are neurogenic, venous, and arterial
- ✓ Primary Raynaud disease—typically involves the digits of the upper extremity and, to a lesser extent, the lower extremity; women are affected more often than men; typical patient is young at disease onset (age <40 years)
- ✓ Secondary Raynaud phenomenon—in contrast to patients with Raynaud disease, these patients are more commonly men with age >40 years

Erythromelalgia

Erythromelalgia is the occurrence of red, hot, painful, and burning digits with exposure to warm temperatures or after exercise. It is not a true vasospastic disorder, but it is associated with color change of the skin. It may be primary (idiopathic) or due to an underlying disorder, most commonly myeloproliferative disorders (eg, polycythemia rubra vera), diabetes mellitus, or small-fiber neuropathy.

Treatment of the primary form includes warm temperature avoidance and aspirin therapy. Therapy with a nonselective β-blocker is helpful for some patients. Symptoms of secondary erythromelalgia are typically relieved with treatment of the underlying disorder.

Key Definition

Erythromelalgia: *occurrence of red, hot, painful, and burning digits with exposure to warm temperatures or after exercise.*

Edema

Lower-extremity edema is commonly encountered in clinical practice and has several potential underlying causes. Noncardiac causes of regional edema usually can be identified from characteristic clinical features.

Lymphedema

Lymphedema can be primary (idiopathic) or due to an underlying disorder. Primary lymphedema (lymphedema praecox) is more common in women (9-fold greater frequency than in men) and typically begins before age 40 years and often before age 20 years. In women, symptoms often first appear at menarche or with the first pregnancy. Edema is bilateral in about one-half of cases (Table 11.5).

Secondary lymphedema is broadly classified into obstructive (postsurgical, postradiation, or neoplastic) and inflammatory (infectious) types.

Obstructive lymphedema due to neoplasm typically begins after age 40 years and often is due to a pelvic neoplasm, lymphoma, or breast cancer. Initial evaluation should include a complete history and physical examination. Contrast medium–enhanced CT imaging of the abdomen and pelvis should be done to evaluate for a neoplastic cause of lymphatic obstruction and proximal venous obstruction of the inferior vena cava or iliac veins. Women should undergo a pelvic examination and Papanicolaou smear. Men should be evaluated for prostate cancer. Inflammatory lymphedema occurs as a result of chronic

Table 11.5 • Differential Diagnosis of Regional Types of Edema

Feature	Venous	Lymphedema	Lipedema
Bilateral	Occasional	±	Always
Foot involved	+	+	–
Toes involved	–	+	–
Thickened skin	–	+	–
Stasis changes	+	–	–

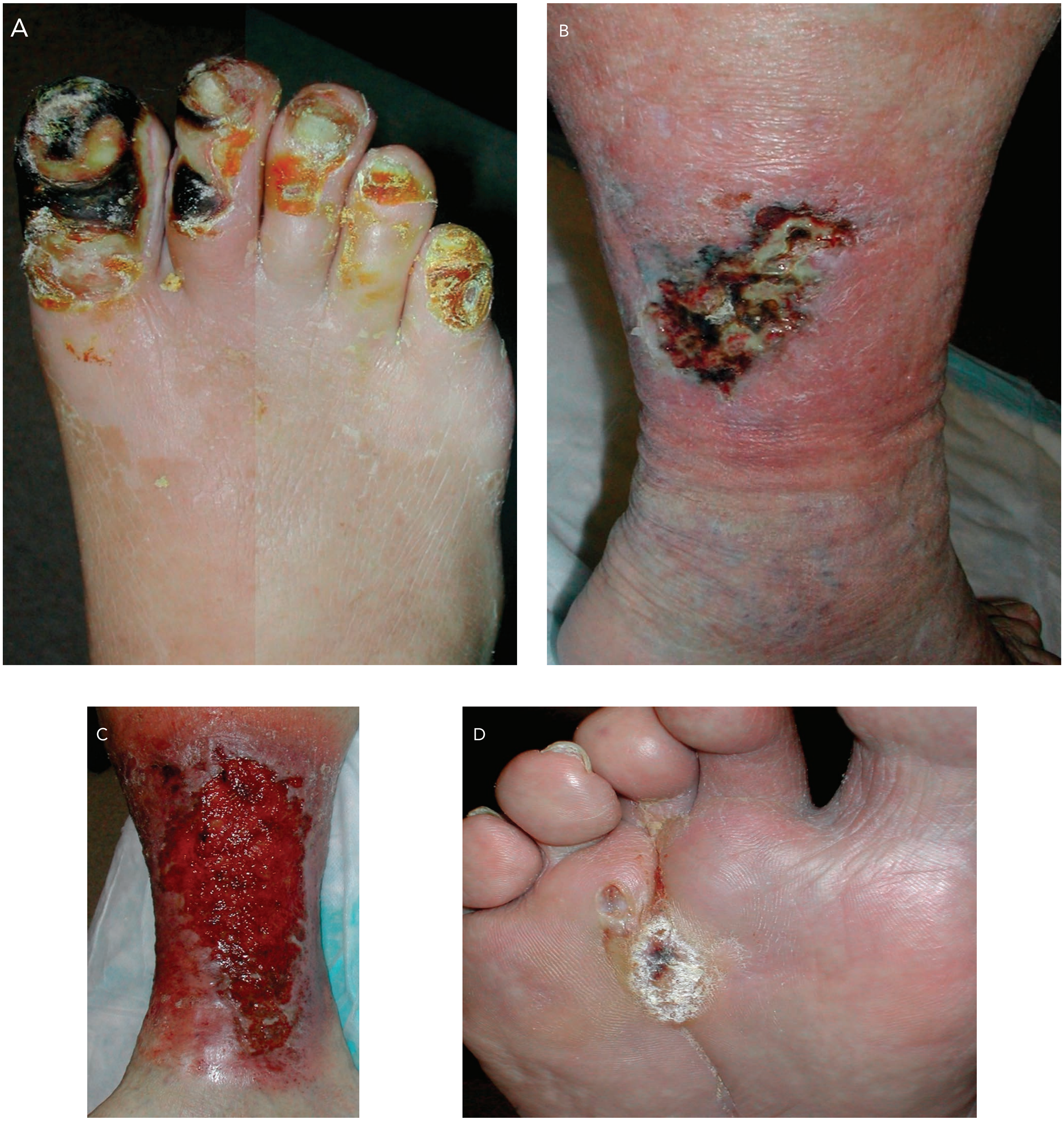


Figure 11.12. *Clinical Features of the 4 Most Common Types of Leg Ulcer. A, Critical limb ischemia due to peripheral artery disease. B, Small-vessel arteriolar disease. C, Venous disease. D, Neurotrophic disease.*

or recurring lymphangitis or cellulitis. Dermatophytosis (tinea pedis) is the most common portal of entry for infection, which is often overlooked. The diagnosis of lymphedema can be evaluated noninvasively with lymphoscintigraphy.

Medical management of lymphedema includes edema reduction therapy using bandage wrapping, followed by daily use of custom-fitted, graduated-compression (usually 40-50 mm Hg) elastic support. Manual lymphatic drainage is a type of massage used in combination with skin care, support and compression therapy, and exercise to manage lymphedema. A combined multimodality approach may substantially reduce excess limb volume and improve quality of life. Dermatophytosis, if present, should be treated with antifungal agents. Weight reduction in obese patients is beneficial. Surgical treatment of lymphedema

Table 11.6 • Clinical Features of the 4 Most Common Types of Leg Ulcer

	Type of Ulcer			
Feature	**Venous**	**Arterial**	**Arteriolar**	**Neurotrophic**
Onset	Trauma ±	Trauma	Spontaneous	Trauma
Course	Chronic	Progressive	Progressive	Progressive
Pain	No (unless infected)	Yes	Yes	No
Location	Medial aspect of leg	Toe, heel, foot	Lateral, posterior aspect of leg	Plantar
Surrounding skin	Stasis changes	Atrophic	Normal	Callous
Ulcer edges	Shaggy	Discrete	Serpiginous	Discrete
Ulcer base	Healthy	Eschar, pale	Eschar, pale	Healthy or pale

(eg, lymphaticovenous anastomosis, lymphedema reduction) may be helpful in carefully selected patients.

Leg Ulcer

The appropriate evaluation and care of skin ulcers involving the lower extremity must begin with identifying and treating the underlying cause when at all possible. Lower-extremity ulcers can be divided into 4 main categories: large-vessel arterial disease, small-vessel arterial disease, venous disease, and neuropathic disease. The cause of lower-extremity ulceration usually can be determined by a careful history and physical examination. Clinical features of the 4 most common types of leg ulcer (Figure 11.12) are summarized in Table 11.6.

II

Questions and Answers

Questions

Multiple Choice (Choose the best answer)

II.1. A 71-year-old woman with hypertension is found incidentally to have atrial fibrillation (AF). She has chronic kidney disease with a creatinine value of 1.5 mg/dL (creatinine clearance, 28 mL/min). What is the next best step in her treatment?

a. Combination of aspirin and clopidogrel
b. Catheter ablation for AF
c. Warfarin therapy for a goal international normalized ratio (INR) of 2.0 to 3.0
d. Dabigatran 150 mg 2 times a day

II.2. A 52-year-old man wears a Holter monitor for intermittent palpitations. He has not had any syncope. The Holter reveals no explanation for his palpitations but shows periods of bradycardia and second-degree heart block (type I) occurring several times at night. What is the next best step?

a. Insertion of a dual-chamber permanent pacemaker
b. Observation, screen for sleep apnea with overnight oximetry
c. Longer-term monitoring with an event recorder or an implantable loop recorder to assess for further evidence of heart block
d. Initiation of theophylline therapy to increase heart rate

II.3. A 64-year-old man had an ST-elevation myocardial infarction and underwent implantation of a drug-eluting stent in the left anterior descending artery. He was noted to have frequent runs of nonsustained ventricular tachycardia during his hospitalization, and β-blocker therapy was initiated with metoprolol succinate and lisinopril. The patient returns to the clinic 3 months later for follow-up. He is feeling well. Echocardiography shows an ejection fraction of 28% with anterior hypokinesis. What is the next best step in his treatment?

a. Implantation of a primary prevention implantable cardioverter-defibrillator (ICD)
b. Amiodarone therapy to suppress ventricular tachycardia and reassess with a Holter monitor in 1 month
c. Catheter ablation
d. Continued medical therapy with angiotensin-converting enzyme inhibitor and β-blocker

II.4. A 45-year-old woman presents to her primary care physician with 4 weeks of fatigue, weight loss, and tremor. In addition, she reports difficulty sleeping and a feeling that her heart is racing. Vital signs are blood pressure of 110/55 mm Hg and heart rate of 132 beats per minute. Physical examination shows that the patient is a thin anxious-appearing woman. Cardiac examination reveals a tachycardic, irregularly, irregular rhythm without murmurs or gallops. There is no evidence of pulmonary edema or peripheral edema. A small goiter is palpated. Blood work is clinically significant for a thyrotropin level <0.01 μIU/L (reference, 0.3-4.2 μIU/L). Electrocardiography shows atrial fibrillation with a rapid ventricular response. What is the best initial treatment for this patient?

a. Methimazole therapy and direct current cardioversion in 1 week
b. Direct current cardioversion as soon as possible
c. Low-molecular-weight heparin therapy and then direct current cardioversion
d. Methimazole therapy along with a β-blocker

II.5. A 62-year-old man reports shortness of breath for the past few months. He states that he is fine at rest but has difficulty walking up 2 flights of stairs. In addition, he has noticed mild lower-extremity swelling. He reports that he has had to sleep in a recliner for the past week to get some rest. The patient denies chest discomfort and chest pain. Incidentally, he notes that his family and friends have asked him whether he has been vacationing because he looks so tan. He has no history of any cardiac problems. His past medical history is significant for a diagnosis of diabetes mellitus 6 months ago. His blood pressure is 110/65 mm Hg; his heart rate is 95 beats per minute. Physical examination shows that the patient is not dyspneic at rest. Lung examination shows mild bibasilar crackles. Cardiac examination shows normal S_1 and S_2 with an S_3 and a soft holosystolic murmur at the apex. Jugular venous pressure is increased to 12 cm. There is 1+ lower-extremity pitting edema; ascites is not present. The patient's skin appears bronze. Echocardiography reveals a dilated left ventricle with an ejection fraction of 30%. Left ventricular filling pressures are increased. The right ventricle is dilated and has mildly decreased systolic function. Both atria are enlarged. The patient has mild-to-moderate mitral regurgitation and trivial tricuspid regurgitation. There is no pericardial effusion. Which of the following is the most likely diagnosis for this patient's cardiomyopathy?

a. Hypertrophic cardiomyopathy
b. Carcinoid heart disease
c. Hemochromatosis
d. Hypereosinophilic myocarditis

II.6. A 28-year-old woman presents with dyspnea on exertion, orthopnea, and bilateral lower-extremity edema. Her symptoms began 4 days ago and have worsened progressively. She underwent a cesarean section 1 week ago because of fetal distress at 40 weeks. Her pregnancy was otherwise uncomplicated. She has no history of cardiac disease. The patient's vital signs are blood pressure of 140/90 mm Hg, heart rate of 114 beats per minute, and oxygen saturation of 92%. Her physical examination shows that she has tachypnea and appears anxious. Lung examination reveals bibasilar crackles. Cardiac examination shows normal S_1 and S_2. An S_3 is present, and a grade II/VI holosystolic murmur is at the apex. Jugular venous pressure is increased to 15 cm with the patient reclining at a 45-degree angle. There is 3+ bilateral pitting edema to the knees. Surgical incision site is dry and intact with no surrounding erythema. Blood work is clinically significant for hemoglobin of 11.3 g/dL, platelets at 400×10^9, and creatinine at 1.0 mg/dL. Electrocardiography shows sinus tachycardia but is otherwise normal. Echocardiography shows a dilated left ventricle with an ejection fraction of 20%. Left ventricular filling pressures are increased. The right ventricle is dilated and has mildly decreased systolic function. Moderate mitral regurgitation and trivial tricuspid valve regurgitation are present. There is no pericardial effusion. Which of the following is the most likely diagnosis?

a. Peripartum cardiomyopathy
b. Pulmonary embolism
c. Postpartum hypertension
d. Amniotic fluid embolism

II.7. An 18-year-old male athlete presents for a preparticipation physical examination for his high school hockey team. He is asymptomatic. On physical examination, his vital signs are normal. An early systolic high-pitched sound is heard at the second intercostal space and is audible at the apex; it is after but very close to S_1 as judged by the carotid upstroke. The patient states that he knows his maternal grandfather just had heart surgery for a valve problem, but he is uncertain as to which valve. What should be the next step in care of this patient?

a. Reassurance and approval to play sports
b. Echocardiography to rule out valvular heart disease
c. Electrocardiography to rule out arrhythmia
d. Recommendation of antibiotic prophylaxis for dental cleaning and examinations

II.8. A 65-year-old man undergoes knee replacement. During physical therapy the day following surgery, he has 3 syncopal episodes in hot weather while working out. The patient has no history of hypertension, diabetes mellitus, or hyperlipidemia. In fact, he has been very active and has been limited only by his recent orthopedic issues. He has no family history of heart disease. He denies knowing about a murmur in the past but has had syncope, without workup, in prior years at least twice. On examination, his blood pressure is 130/80 mm Hg; carotid upstroke is palpable and has a shudder in the contour. There is a systolic murmur, which becomes louder and earlier with Valsalva maneuver. What is the most likely diagnosis for this patient?

a. Hypertrophic cardiomyopathy
b. Vasovagal syncope
c. Severe aortic stenosis
d. Mitral regurgitation

II.9. A 45-year-old woman with long-standing dilated cardiomyopathy returns to the clinic for follow-up. She endorses considerable symptoms of dyspnea walking around her home and feels well only when she is at rest. The patient's current medications include lisinopril 10 mg daily, metoprolol succinate 50 mg daily, and furosemide 40 mg daily. What is the classification of her functional class and stage?

a. New York Heart Association (NYHA) class IV, stage D
b. NYHA class III, stage B
c. NYHA class III, stage C
d. NYHA class IV, stage C

II.10. A 42-year-old man returns to the clinic after an evaluation in the emergency department for pneumonia. A computed tomographic scan shows cardiomegaly. The scan culminates in echocardiography that shows global hypokinesis (ejection fraction, 40%). The patient has recovered from his pneumonia, exercises regularly, and has no symptoms. On examination, his blood pressure is 152/92 mm Hg, and he is otherwise healthy. His laboratory data are unrevealing. What is the next best treatment to offer him?

a. No treatment
b. Diltiazem
c. Loop diuretic
d. β-Blocker and angiotensin-converting enzyme inhibitor

II.11. A 72-year-old man returns to the clinic with reports of new lower-extremity edema for the past 4 months and exertional fatigue and dyspnea for the past 3 weeks. He has a past medical history of long-standing hypertension, obesity, and glucose intolerance. His current treatment includes candesartan/hydrochlorothiazide 32 mg/25 mg. Electrocardiography is obtained and shows voltage criteria for left ventricular hypertrophy, confirmed by subsequent echocardiography. His diagnosis is established as new-onset heart failure with preserved ejection fraction (HFpEF). What treatment would be expected to improve overall survival for this patient?

a. Aldosterone antagonism
b. Dihydropyridine calcium channel blockade
c. Transition from angiotensin receptor blocker to angiotensin-converting enzyme inhibitor
d. No treatment has been shown to improve survival for patients with HFpEF.

II.12. A 59-year-old black woman presents with a medical history remarkable for obesity and a sedentary lifestyle, diet-controlled type 2 diabetes mellitus without complications, gout with allopurinol therapy with no recent recurrences, and hyperlipidemia with statin therapy. Blood pressure is 139/88 mm Hg at her general medical examination. She subsequently had ambulatory blood pressure monitoring that confirmed the diagnosis of stage 1 hypertension. In addition to lifestyle modifications, pharmacologic management is now indicated. What drug is the best choice for treatment of this patient's hypertension?

a. Lisinopril
b. Spironolactone
c. Chlorthalidone
d. Atenolol

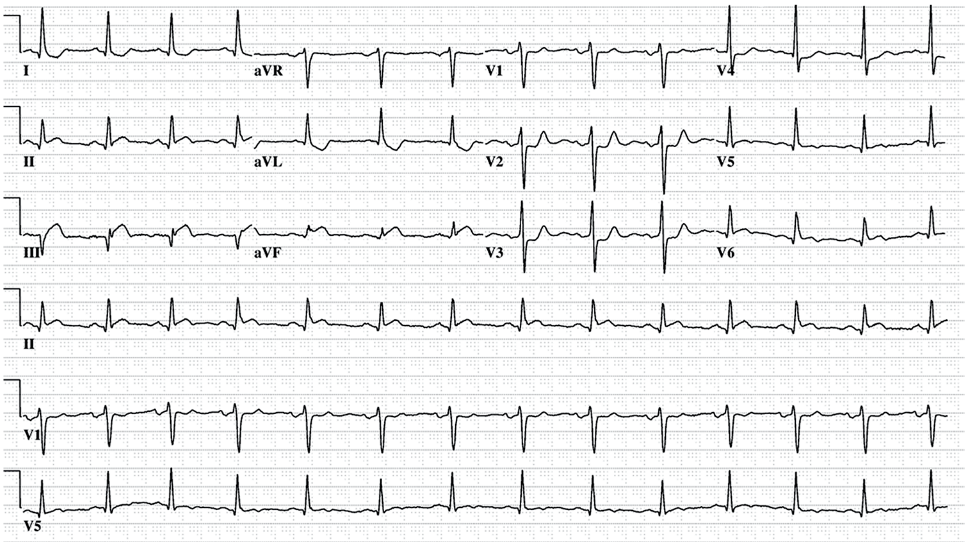


Figure II.Q15.

II.13. A 77-year-old man with asymptomatic coronary disease, obstructive sleep apnea treated with continuous positive airway pressure, and hypertension is seen in follow-up for medication refills. He takes hydrochlorothiazide 25 mg daily, lisinopril 20 mg daily, and metoprolol succinate 50 mg daily. His in-office blood pressure is 128/79 mm Hg. His pulse is 55 beats per minute. What is the next best step in management?

a. Increase in lisinopril dose
b. Increase in metoprolol dose
c. Addition of amlodipine
d. Continuation of current medications and doses

II.14. A 36-year-old woman with hypertension that historically has been well controlled with lisinopril therapy is planning to become pregnant. What is the best next step in management?

a. Discontinue lisinopril and add methyldopa.
b. Discontinue lisinopril and add clonidine.
c. Discontinue lisinopril and add hydrochlorothiazide.
d. Discontinue lisinopril and add losartan.

II.15. A 60-year-old woman presents with acute-onset chest pain for 45 minutes with the electrocardiography findings as shown in Figure II.Q15.

Examination shows heart rate at 105 beats per minute; blood pressure, 95/60 mm Hg; increased jugular venous pressure (JVP); clear lungs; and no murmurs or gallops. Which of the following treatments is a class III (evidence or general agreement that the treatment is not useful or effective) indication?

a. Intravenous fluids
b. Dobutamine
c. Nitroglycerin
d. Dopamine

II.16. What is the correct antiplatelet regimen for patients with ST elevation myocardial infarction at the time of fibrinolysis?

a. Aspirin + prasugrel
b. Aspirin + ticagrelor
c. Aspirin + clopidogrel
d. Aspirin + tirofiban

II.17. A 35-year-old man presents to the urgent care service with the chief report of chest pain that came on during the night and has been present for 12 hours. It awoke him from sleep and is worse when he lies on his back and left side and when he takes a deep breath. He has achieved some relief by sitting up and leaning forward. He has a cough and sore throat that started a week ago and are getting better. He is unsure if he has had a fever but has been feeling warm. Examination shows the following results.

Blood pressure, 168/96 mm Hg
Heart rate, 115 beats per minute
Jugular venous pressure not visible because of body habitus
Carotid blood flow brisk and full
Lungs clear
Tachycardia, with murmur or summation gallop, that is louder with the patient in the left lateral decubitus position and almost disappears in the seated positon
White blood cell count, 13,000/μL with predominance of lymphocytes
Troponin negative
Chest radiograph showing poor inspiration and borderline cardiomegaly
Electrocardiography as shown in Figure II.Q17

What is the next best step in management?

a. Percutaneous cardiac intervention (PCI) for coronary angiography and PCI if indicated
b. High-dose ibuprofen therapy 800 mg 3 times daily, pantoprazole 40 mg daily, and colchicine 1 mg immediately, then 0.6 mg daily
c. Echocardiography
d. Cardiac computed tomography (CT)

II.18. A 65-year-old diabetic man underwent aortic valve replacement for calcific degenerative aortic stenosis and 3-vessel coronary bypass grafting for symptomatic coronary artery disease 2 months ago. He was doing well in cardiac rehabilitation until 2 weeks ago, when he noted increased fatigue, dyspnea, and peripheral edema. On examination, the following results are observed.

Jugular venous pressure raised to above the clavicle at midneck with the patient seated and with rise during inspiration and rapid y waves noted

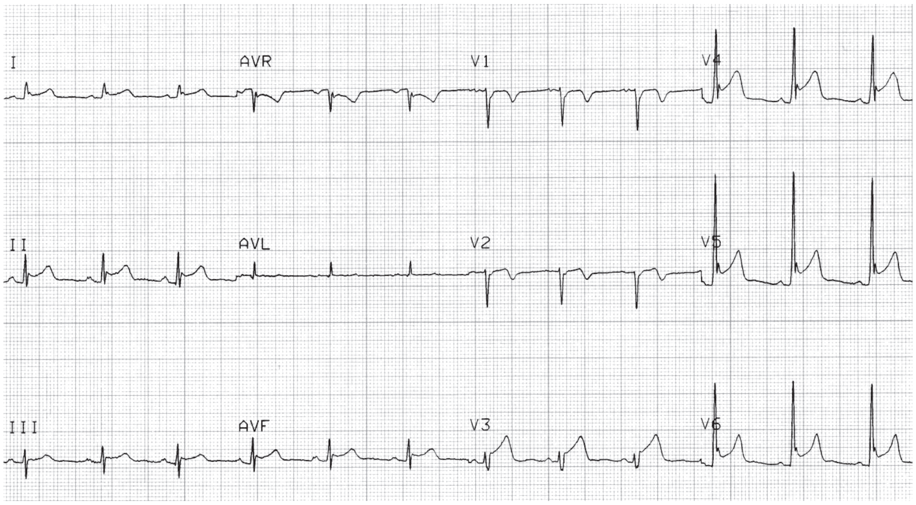


Figure II.Q17.

Carotid pulses brisk, no bruits

Cardiac examination reveals a soft grade 2 systolic ejection murmur along the right sternal boarder, with distant heart tones

Midsternotomy is well healed

Abdomen shows moderate abdominal obesity, no bruits, and no hepatosplenomegaly

Extremity examination reveals brawny form, induration of both lower extremities to the knees, with venous status changes

Laboratory testing shows erythrocyte sedimentation rate of 30 seconds, high-sensitivity C-reactive protein concentration of 13.8 mg/L, and NT-pro brain natriuretic peptide concentration of 819 pg/mL

Electrocardiography as shown in Figure II.Q18A

Chest radiograph as shown in Figure II.Q18B

What is the next best step in management?

a. Echocardiography, high-sensitivity C-reactive protein test, and erythrocyte sedimentation rate
b. Hemodynamic cardiac catheterization
c. Cardiac magnetic resonance imaging
d. Initiation of prednisone therapy

II.19. A 33-year-old man presents for a "physical" as required by his employer. He reports no problems. On examination, a crisp systolic click is heard immediately after S_1. No murmur is heard. The patient recalls that he was told he had "something" wrong with a valve during a sports participation physical at age 16 years, with subsequent evaluation by a pediatric cardiologist who told him his valve had normal function. He was cleared to play sports. His blood pressure is normal in both arms and his pulses are equal throughout. Which of the following is the most appropriate next step in management?

a. Return to the clinic in 1 year for examination. No imaging is needed because there is no murmur or symptoms.
b. Computed tomographic scan of the aorta to evaluate for coarctation of the aorta
c. Echocardiography to assess aortic valve function and ascending aorta dimension
d. Echocardiography to assess mitral valve function and left ventricular dimension

II.20. A 62-year-old man with history of symptomatic bicuspid aortic valve stenosis recently underwent aortic valve replacement with

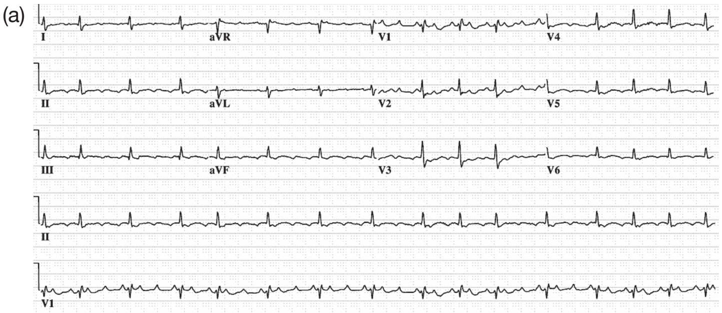


Figure II.Q18A.

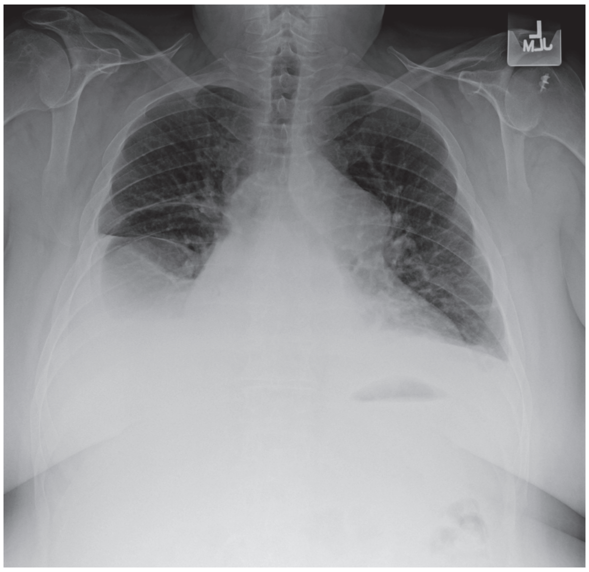
(b)


Figure II.Q18B.

a 25-mm St. Jude Medical bileaflet mechanical prosthesis. He has no history of atrial fibrillation, congestive heart failure, transient ischemic attack or stroke, or hypercoagulable condition. His hospital discharge medications should include which of the following?

a. Warfarin with an international normalized ratio (INR) goal of 2.5 and no aspirin
b. Warfarin with INR goal of 3.0 and no aspirin
c. Warfarin with INR goal of 3.0 plus aspirin 81 mg daily
d. Apixaban 5 mg twice daily plus aspirin 81 mg daily

II.21. A 25-year-old man presents with gangrene of the tips of multiple upper- and lower-extremity digits. He describes a history of foot claudication symptoms and prior superficial venous thrombophlebitis. He is also a heavy smoker. He is admitted to the hospital, undergoes angiography, and receives the diagnosis of thromboangiitis obliterans (Buerger disease). What is the next best step in management?

a. Arterial bypass grafting
b. Angioplasty
c. Thrombolysis
d. Tobacco cessation

II.22. A 75-year-old man with a history of tobacco abuse and type 2 diabetes mellitus presents for a general evaluation. On examination, he has a pulsatile abdominal mass and bruit. Ultrasonography shows an abdominal aortic aneurysm of 5.7 cm. What is the next best step in management?

a. Ultrasonography in 6 months
b. Tobacco cessation
c. Surgical evaluation
d. Statin therapy

Answers

II.1. Answer c.

Warfarin for a goal INR of 2.0 to 3.0. Anticoagulation is warranted given the patient's CHA_2DS_2-VASc (*c*ongestive heart failure, *h*ypertension, *a*ge ≥65 years, *d*iabetes mellitus, previous *s*troke or transient ischemic attack, *v*ascular disease, *a*ge ≥75 years, and female *s*ex) score of 3 (age, sex, and hypertension). Dabigatran would require dose reduction given her creatinine clearance. Warfarin is the best of the listed options.

II.2. Answer b.

Since these episodes are asymptomatic and occur at night, no further treatment is needed. Sleep apnea is a common cause of such rhythm disturbances at night, and it is reasonable to screen for it.

II.3. Answer a.

This patient qualifies for a primary prevention ICD. While amiodarone is useful in reducing ventricular tachycardia burden and ICD shocks, it does not offer a mortality benefit in these patients. Catheter ablation can be useful when they have ongoing arrhythmia, especially when it is refractory to medications, but the first priority should be device implantation.

II.4. Answer d.

Atrial fibrillation is the most common arrhythmia occurring in the clinical setting of hyperthyroidism. β-Blocker therapy should be initiated early, along with treatment of hyperthyroidism (which may involve a thionamide, radioactive iodine, or surgery). Patients may have restoration of sinus rhythm spontaneously after they achieve a euthyroid state. Direct current cardioversion may be needed if there is no spontaneous return of sinus rhythm but should only be attempted after the patient is in a euthyroid state. Anticoagulation may be indicated for the atrial fibrillation but would not be a better option than β-blockade or treatment of the hyperthyroid state. Immediate cardioversion would be indicated only in a physiologically unstable patient with atrial fibrillation.

II.5. Answer c.

The patient presents with heart failure, according to his clinical symptoms and signs. His echocardiogram is consistent with a dilated cardiomyopathy. In addition, he has new-onset diabetes with evidence of bronze skin coloration. All of these point to hemochromatosis as the cause of his cardiomyopathy. Hemochromatosis is a condition of iron overload in which iron may deposit in multiple organs including the liver, the pancreas (causing diabetes mellitus), the skin (causing bronzing), and the heart. Iron deposition in the heart leads to dilated cardiomyopathy. Hypertrophic cardiomyopathy is a condition of thick walls and is not a dilated cardiomyopathy. Carcinoid heart disease typically affects the valves on the right side of the heart, leading to clinically significant tricuspid valve and pulmonic valve regurgitation with some stenosis. Left-sided heart valves may be involved when a right-to-left shunt is present (eg, from an atrial septal defect or patent foramen ovale). Hypereosinophilic myocarditis typically presents with embolic phenomenon due to deposition of thrombi in the apices of the ventricles, most commonly the left ventricle. This condition, left untreated, may lead to heart failure due to a restrictive cardiomyopathy rather than a dilated cardiomyopathy.

II.6. Answer a.

This patient presents with typical heart failure symptoms 1 week after a cesarean section. Her echocardiogram is consistent for dilated cardiomyopathy with biventricular involvement. She has moderate mitral valve regurgitation due to acute left ventricular dilatation. Peripartum cardiomyopathy is a relatively rare form of systolic heart failure that most commonly occurs during the first month after delivery. The left ventricle is usually dilated, and left ventricular ejection fraction is reduced. The right ventricle may be involved in more severe cases. Pulmonary embolism must always be considered for a woman who presents with shortness of breath during pregnancy or the postpartum period. However, pulmonary embolism would potentially result in right-sided heart failure, not biventricular heart failure. Postpartum hypertension has been observed in as many as 20% of women within 6 weeks of delivery. Increased blood pressure may be due to a combination of factors, including administration of a large volume of intravenous fluids during cesarean delivery. Blood pressure usually normalizes without treatment within 6 weeks postpartum and with no effect on cardiac chamber size or systolic function. For this patient, blood pressure is most likely increased because of volume overload due to acute systolic heart failure superimposed on the usual postpartum volume overload. Amniotic fluid embolism is a rare catastrophic complication of pregnancy that occurs either during pregnancy or very shortly after delivery. Most patients present with hypotension, hypoxia, and disseminated intravascular coagulation, and the condition rapidly progresses to cardiorespiratory collapse.

II.7. Answer b.

This patient is likely to have an ejection sound or ejection click. One must rule out the presence of a bicuspid aortic valve and the potential to be associated with an aortic aneurysm. If a bicuspid valve is present, he will need to be monitored lifelong for aortic valve disease and ascending aortic aneurysm development. As long as the aorta is normal, he can participate in sports. Additionally, other first-degree family members then need to be screened for bicuspid aortic valve, if it is present in him. Reassurance would not be appropriate because, on the basis of the auscultation finding, he may have a cardiac condition where participation in sports could be dangerous. There is nothing on examination or history to suggest an arrhythmia, so electrocardiography would not be the next best step. Finally, this patient does not meet the requirements to recommend prophylactic antibiotics before dental procedures.

II.8. Answer a.

The patient's blood volume is probably somewhat depleted because of surgery, which exacerbates the physiologic factors of dynamic outflow tract obstruction and leads to syncope. The history of past syncope also suggests this diagnosis. Echocardiography would be appropriate to confirm the suspected diagnosis. Although vasovagal syncope in this setting is common, the murmur found in this patient would not be expected. Aortic stenosis and mitral regurgitation are incorrect answers because their associated murmurs would become softer with Valsalva, which was not seen in this patient.

II.9. Answer c.

The NYHA classification is a functional one and allows patients to be placed in 1 of 4 classes on the basis of degree of limitation they note during activity. This patient would be viewed as class III because she has marked limitation during less than normal activity, yet she feels well at rest. She would be viewed as stage C because she has current heart failure symptoms that are managed with medical treatment.

II.10. Answer d.

This patient has structural heart dysfunction but no symptoms of heart failure at present, characterized as stage B. Patients with stage B should be offered treatment without waiting for symptom development. Negative inotropic calcium channel blockade would be contraindicated. A loop diuretic is not indicated.

II.11. Answer d.

At present, treatment of HFpEF is limited to symptomatic management. Treatments that affect survival in heart failure with reduced ejection fraction have not been shown to have similar impact in HFpEF.

II.12. Answer c.

In black adults with hypertension but without heart failure or chronic kidney disease, including those with diabetes mellitus, the initial antihypertensive treatment should include a thiazide-type diuretic or calcium channel blocker alone or in combination.

II.13. Answer d.

This patient is at his goal for hypertension management. For adults with hypertension and known cardiovascular diseases or a 10-year atherosclerotic cardiovascular disease event risk of 10% or higher, a blood pressure target of less than 130/80 mm Hg is recommended. Therefore, his current medication regimen can be continued.

II.14. Answer a.

Women with hypertension who become pregnant or are planning to become pregnant should receive therapy transition to methyldopa, nifedipine, or labetalol, or a combination, during pregnancy. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and direct renin inhibitors are contraindicated in pregnancy.

II.15. Answer c.

Electrocardiography demonstrates inferior ST-elevation myocardial infarction, and physical examination disclosed increased JVP with clear lungs. In this scenario, one must suspect right ventricular infarction. The increased JVP provides preload to the failing right ventricle. Of the available options, nitroglycerin could reduce this preload and worsen hemodynamics. Therefore, nitroglycerin would be a class III indication in this setting.

II.16. Answer c.

Clopidogrel is the only P2Y12 inhibitor that has been used in the clinical setting of fibrinolysis and therefore is the only agent approved for this use.

II.17. Answer b.

Pericarditis is a clinical diagnosis that requires at least 2 of 4 components: characteristic pleuritic chest pain, pericardial friction rub, typical electrocardiographic changes, and new or worsening pericardial effusion. This patient has 3 of the 4 components. Echocardiography would not rule out pericarditis. Potentially, it would be harmful to take this patient to the catheterization laboratory, and CT would carry a small risk of radiation and unnecessary testing in this classic clinical presentation. For this patient, the diagnosis is clear, and additional testing is not necessary.

II.18. Answer a.

The next best test that likely will lead to the clinically suspected diagnosis of constrictive pericarditis is echocardiography, which will give the required hemodynamic information. With the patient's clinical history of recent cardiac operation, heart failure presentation (right-sided congestion with peripheral edema), elevated inflammatory marker levels, low voltage on electrocardiography, and pleural effusion, the clinical suspicion is high for postcardiotomy syndrome, which is a form of constrictive pericarditis. Prednisone may be indicated, but for a diabetic patient, the diagnosis needs to be cemented first.

II.19. Answer c.

The examination description is most consistent with a bicuspid aortic valve that is still pliable. On examination, there is no evidence of serious valvular obstruction, but echocardiography is indicated for evaluation because a patient with normally functioning bicuspid valves is at risk for progressive ascending aortic enlargement, which would have no symptoms. In addition, diastolic murmurs of aortic insufficiency are sometimes difficult to auscultate; the valve function should be completely assessed with echocardiography. The click is not consistent with the click of mitral valve prolapse, which is a mid-systolic click. Although the risk of coarctation is about 5% for a patient with bicuspid valve, this patient is not likely to have a coarctation because he has normal blood pressure and pulses. In addition, he was evaluated previously by a pediatric cardiologist at age 16 and cleared to play sports without intervention. However, echocardiography is a useful tool for investigation of coarctation of the aorta. If there were any concerns raised on echocardiography, computed tomography could be ordered (or preferably magnetic resonance imaging to avoid radiation) to evaluate the aorta further. Patients with bicuspid aortic valve should be counseled that their first-degree relatives have increased risk of bicuspid aortic valve and should be screened with echocardiography.

II.20. Answer c.

All patients with bileaflet mechanical heart valve prostheses require both anticoagulant and antiplatelet therapies indefinitely to reduce the risk of prosthetic thrombosis. Patients with bileaflet mechanical aortic valve prosthesis are at the lowest risk for prosthetic thrombosis compared with patients who have mechanical prostheses in other positions. Patients with a bileaflet mechanical heart valve prosthesis and no risk factors (ie, atrial fibrillation, congestive heart failure, transient ischemic attack or stroke, or hypercoagulable condition) should be treated with warfarin with an INR goal of 2.5 and aspirin 75 to 100 mg daily indefinitely. Warfarin with an INR goal of 2.5 and no aspirin is incorrect because indefinite low-dose aspirin therapy is recommended for every patient with a mechanical heart valve prosthesis. Warfarin with an INR goal of 3.0 plus aspirin 81 mg daily is incorrect because the

INR goal for patients with a bileaflet mechanical aortic valve prosthesis and no risk factors is 2.5. Apixaban 5 mg twice daily plus aspirin 81 mg daily are incorrect because both oral direct thrombin and factor Xa inhibitors are contraindicated as anticoagulant therapy for patients with mechanical prosthetic heart valves because of increased risk of thrombosis and thromboembolism compared with patients treated with warfarin anticoagulation.

II.21. Answer d.

The treatment of thromboangiitis obliterans is limited to tobacco cessation, wound care, limb protection, and, when needed, amputation. Revascularization techniques such as arterial bypass grafting, angioplasty, and stenting are rarely possible or effective.

II.22. Answer c.

Abdominal aortic aneurysms greater than 5.5 cm should be evaluated by a surgeon. Repair is recommended for aneurysms of 5.5 cm or more or with a growth rate of 0.5 cm or more per year, atheroemboli, or any suggestion of instability. Waiting 6 months to repeat an ultrasonographic examination would not be appropriate for this patient, given the aneurysms' size. Smoking cessation and statin therapy would likely be important for this patient; however, the most urgent intervention should be surgical evaluation.

Section III

Endocrinology

12 Calcium and Bone Metabolism Disorders

MATTHEW T. DRAKE, MD, PHD

Hypercalcemia

The causes of hypercalcemia are categorized into either parathyroid hormone (PTH) dependent or PTH independent.

PTH-Dependent Hypercalcemia

Primary Hyperparathyroidism

Etiologic Factors

Primary hyperparathyroidism is the most common cause of hypercalcemia in ambulatory patients. A single parathyroid adenoma is its cause in 85% of patients, and multiglandular disease is the cause in the rest. Parathyroid carcinoma is a rare cause of hypercalcemia. Primary hyperparathyroidism may be sporadic or familial. Familial hyperparathyroidism is usually multiglandular and most commonly a manifestation of multiple endocrine neoplasia (MEN) type 1 or MEN type 2 syndromes.

Clinical Features

Most patients with hyperparathyroidism are asymptomatic and are identified with routine laboratory testing. Symptoms of hypercalcemia include polyuria, polydipsia, constipation, fatigue, and abdominal pain. Hypercalciuria can cause nephrolithiasis and nephrocalcinosis. Skeletal manifestations include osteopenia or osteoporosis and, in severe disease, bone pain, fractures, and osteitis fibrosa cystica (bone pain and characteristic areas of periosteal bone resorption).

Diagnosis

Elevated serum calcium and PTH levels are hallmarks of primary hyperparathyroidism. The serum PTH level is usually increased but may be inappropriately normal for the degree of hypercalcemia present. Serum phosphate concentrations are normal or low. Urinary calcium excretion is high-normal or high; this test is also useful to assess risk of nephrolithiasis and exclude disorders characterized by low urinary calcium excretion (eg, familial hypocalciuric hypercalcemia, thiazide diuretic use). Characteristic skeletal radiographic changes of long-standing or advanced disease include subperiosteal bone resorption, a salt-and-pepper appearance of the skull, and osteitis fibrosa cystica. Renal stones or nephrocalcinosis may be visible on abdominal radiographs.

Therapy

Surgical parathyroidectomy is the treatment of choice. Conservative therapy may be indicated for mild uncomplicated disease, especially in elderly patients. Indications for surgical intervention are listed in Box 12.1. Imaging studies are helpful for guiding the surgeon, but they do not help in diagnosis. Preoperative imaging (parathyroid sestamibi scanning or ultrasonography) often identifies a solitary parathyroid adenoma, allowing minimally invasive surgery. Transient, mild hypocalcemia is common in the early postoperative period. However, in patients with severe, preexisting parathyroid-induced bone disease, correction of hyperparathyroidism may lead to marked and prolonged hypocalcemia due to so-called hungry bone syndrome.

The editors and authors acknowledge the contributions of Marius N. Stan, MD, to the previous edition of this chapter.

Box 12.1 • Indications for Surgical Intervention for Primary Hyperparathyroidism

Age <50 years

Serum calcium level more than 1 mg/dL above the upper limit of the reference range

Nephrolithiasis

Osteoporosis (to include DXA at spine, hips, and distal radius)

Renal insufficiency (creatinine clearance <60 mL/min)

Familial Hypocalciuric Hypercalcemia

Familial hypocalciuric hypercalcemia is an autosomal dominant disorder resulting from an altered set point of the calcium-sensing receptor in the parathyroid glands and renal tubules. It manifests as mild, asymptomatic hypercalcemia in a patient with a normal or slightly increased PTH level, low urinary calcium concentration, and often a family history positive for hypercalcemia. The diagnosis is strongly supported by a ratio of urinary calcium to creatinine clearance that is less than 0.01, distinguishing it from primary hyperparathyroidism. Genetic testing is clinically available. Parathyroid surgery is not indicated because complications associated with hyperparathyroidism do not develop.

KEY FACTS

✓ Primary hyperparathyroidism—most common cause of hypercalcemia in ambulatory patients

✓ Hyperparathyroidism—usually asymptomatic; identified with laboratory testing

✓ Hallmarks of primary hyperparathyroidism—elevated levels of serum calcium and (usually) PTH

✓ Severe preexisting parathyroid-induced bone disease—awareness of this disease is important; correction of hyperparathyroidism may cause marked, prolonged hypocalcemia (from hungry bone syndrome)

✓ Familial hypocalciuric hypercalcemia—ratio of urinary calcium to creatinine clearance is <0.01 (unlike in primary hyperparathyroidism)

Thiazide-Induced Hypercalcemia

Mild hypercalcemia may occur in patients taking thiazide diuretics. The hypercalcemia is multifactorial (dehydration, decreased renal calcium clearance, and possibly increased PTH secretion). PTH levels are inappropriately normal or mildly increased. Unless it is coexistent with primary hyperparathyroidism, the hypercalcemia usually resolves within a few weeks after discontinuation of the drug.

Lithium-Induced Hypercalcemia

Lithium raises the threshold for serum calcium to inhibit PTH secretion. PTH levels are inappropriately normal or mildly increased. The hypercalcemia is likely to resolve after discontinuation of lithium therapy. However, 4-gland parathyroid hyperplasia can occur with long-term lithium administration, and hypercalcemia then may persist despite discontinuation of lithium therapy.

PTH-Independent Hypercalcemia

Hypercalcemia of Malignancy

Hypercalcemia of malignancy often develops acutely and may be severe and life-threatening. It is the most common cause of hypercalcemia in hospitalized patients. It results from 1 of 3 mechanisms: 1) the destructive effects of skeletal metastases through local cytokines, 2) the effect of increased production of 1,25-dihydroxyvitamin D (the active form of vitamin D) by some tumors (eg, lymphomas), or 3) the paraneoplastic effect of a malignancy through increased production of PTH-related peptide. Serum PTH is suppressed in all cases of hypercalcemia due to malignancy.

Vitamin D Intoxication

Hypercalcemia, hypercalciuria, renal insufficiency, and soft tissue calcification can result from prolonged intake of high levels of vitamin D. Because vitamin D is a fat-soluble vitamin and thus is stored in fat, this condition may persist for months after vitamin D supplementation has been discontinued.

Sarcoidosis, Granulomatous Disorders, and Lymphoma

Hypercalcemia and hypercalciuria in sarcoidosis, granulomatous disorders, and lymphoma are due to increased 1α-hydroxylase activity within the cells of the granuloma or lymphoma, which can autonomously generate 1,25-dihydroxyvitamin D. The serum 25-hydroxyvitamin D level is typically normal, whereas the 1,25-dihydroxyvitamin D level is increased. The PTH level is low, and the serum phosphorus level may be normal or elevated. The hypercalcemia is responsive to treatment of the underlying disease and glucocorticoid therapy (which inhibits 1α-hydroxylase activity).

Miscellaneous Causes

Hyperthyroidism enhances bone turnover and may lead to net bone loss. Hypercalcemia and, more often, hypercalciuria may be present. The hypercalcemia resolves with the treatment of thyrotoxicosis.

Addison disease can cause symptomatic hypercalcemia related to dehydration and increased albumin concentration. The hypercalcemia is reversible with glucocorticoid therapy.

Management of Hypercalcemia

When feasible, treatment of the primary cause of hypercalcemia is the best intervention. Glucocorticoids are the drugs of choice for the hypercalcemia of granulomatous disorders. Humoral hypercalcemia of malignancy may respond to complete resection of the tumor. In severe hypercalcemia or hypercalcemia in which the primary cause is not immediately treatable, calcium concentrations should be decreased. Aggressive rehydration with volume expansion is necessary because most patients are dehydrated and because hydration also promotes calciuresis. Loop diuretics (used *after* volume expansion) promote renal calcium excretion. A single-dose, intravenous infusion of pamidronate or zoledronic acid or a single subcutaneous injection of denosumab inhibits both bone resorption and the mobilization of calcium from bone and has a marked, prolonged effect on calcium concentrations. For patients with persistent parathyroid disease not amenable to surgery, calcimimetic agents (eg, cinacalcet) are an acceptable medical option. Dialysis with a low-calcium dialysate bath is reserved for patients with renal failure or when a rapid decrease in calcium is needed that cannot be achieved by the above methods.

Hypocalcemia

Etiologic Factors

The causes of hypocalcemia include hypoparathyroidism, decreased vitamin D production, vitamin D resistance, and disorders associated with decreased mobilization of calcium from bone or increased calcium deposition in tissues.

Hypoparathyroidism may be due to decreased PTH production (the most common cause) or to resistance of the target tissue to the actions of PTH. The parathyroid glands may be damaged during thyroidectomy, or they may be excised completely for the treatment of primary hyperparathyroidism due to parathyroid hyperplasia. Postoperative hypoparathyroidism may be transient or permanent. It appears within hours after the operation and if transient can take days to weeks for full recovery. Other, less common causes of decreased PTH secretion are an autoimmune or infiltrative process involving the parathyroid glands (hemochromatosis or Wilson disease), a congenital defect (DiGeorge syndrome), or hypomagnesemia (due to proton pump inhibitor or diuretic use, malabsorption, or malnutrition), which impairs the secretion and action of PTH.

Pseudohypoparathyroidism is characterized by end-organ (kidney and bone) resistance to the actions of PTH as a result of a receptor or postreceptor defect. In 1 type—Albright hereditary osteodystrophy— patients have a characteristic appearance: short stature, round face, obesity, short fourth metacarpal bones, and mild mental retardation. A defect in the Gs alpha subunit downstream of the PTH receptor is commonly identified. Patients have hypocalcemia, hyperphosphatemia, and an elevated PTH level.

Pseudopseudohypoparathyroidism is a variant in which patients have the same characteristic phenotype as the patients with Albright hereditary osteodystrophy but do not have the biochemical abnormalities.

Vitamin D deficiency may be caused by malnutrition, malabsorption, and liver or kidney disease. In acute or chronic renal failure, the pathogenesis of hypocalcemia is thought to be multifactorial, resulting from hyperphosphatemia and decreased 1,25-dihydroxyvitamin D production. In vitamin D deficiency, hypocalcemia triggers secondary hyperparathyroidism with renal phosphate wasting.

Increased calcium deposition in tissue occurs in *osteoblastic metastases* (eg, prostate cancer) and in *hungry bone syndrome* occurring after parathyroidectomy for hyperparathyroidism with severe bone disease. Hypocalcemia and soft tissue calcification may also occur in *acute pancreatitis*. Increased calcium elimination is associated with the use of *loop diuretics*. An inability to maintain a normal serum calcium level can also occur after the administration of potent antiresorptive drugs, particularly for patients with preexisting vitamin D deficiency.

Laboratory and Clinical Features

Hypoparathyroidism leads to decreased mobilization of calcium from bone, decreased renal calcium reabsorption, decreased renal phosphate excretion, and decreased renal production of 1,25-dihydroxyvitamin D, with subsequent hypocalcemia and hyperphosphatemia. In hypoparathyroidism, the PTH level is low or inappropriately normal in the presence of hypocalcemia. In contrast, the PTH level is increased in pseudohypoparathyroidism.

Hypocalcemia is often manifested by a tingling sensation in the fingers, perioral numbness, muscle cramping, or a positive Chvostek sign (facial nerve hyperirritability) or Trousseau sign (characteristic hand posture after blood pressure cuff inflation due to nerve hyperirritability and muscle spasm). Symptoms of hypocalcemia reflect its severity and rate of development. Laryngeal stridor and convulsions can occur when hypocalcemia is severe. Basal ganglia calcification, cataract formation, and benign intracranial hypertension can result from chronic hypoparathyroidism. QT-interval prolongation may be present. Mucocutaneous candidiasis may develop as a manifestation of polyglandular autoimmune syndrome type I (ie, hypoparathyroidism, adrenal insufficiency, and mucocutaneous candidiasis).

Diagnostic Approach

Correct assessment of calcium requires a mathematical correction of the total calcium value based on serum albumin level or the measurement of ionized calcium. This assessment should be followed by measurement of the serum PTH level. In a hypocalcemic patient, a low PTH level is diagnostic of hypoparathyroidism. A high PTH level is suggestive of vitamin D deficiency or pseudohypoparathyroidism. Abnormal serum concentrations of creatinine and magnesium help identify renal failure and magnesium deficiency states.

Therapy

For acute severe hypocalcemia, urgent treatment with intravenous calcium is indicated to prevent tetany, laryngeal stridor, or convulsions. Extravasation of calcium can cause severe tissue necrosis, and therefore administration through central intravenous access (*not* peripheral) is urged. Intravenous calcium should be infused slowly over 5 to 10 minutes. Continuous electrocardiographic monitoring is essential.

For long-term treatment of hypocalcemia, oral calcium supplements and vitamin D are given. In hypoparathyroidism and renal insufficiency, the PTH-mediated conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D occurs only inefficiently. Therefore, the preferred form of vitamin D therapy is calcitriol (the active form of vitamin D). Thiazide diuretics are used to decrease the risk of marked hypercalciuria, and oral phosphate binders may be given to control hyperphosphatemia. It is critical to monitor therapy closely since patients are at risk for hypercalciuria, nephrolithiasis, and nephrocalcinosis. Therapeutic doses are adjusted to keep the serum level of calcium *just below* the lower limit of the reference range and the urinary level of calcium at less than 300 mg in 24 hours.

KEY FACTS

- ✓ Thiazide diuretics—their use is a cause of mild hypercalcemia with inappropriately normal or mildly increased PTH levels; it usually resolves within weeks after stopping the drug
- ✓ Hypercalcemia of malignancy—most common cause of hypercalcemia in hospitalized patients; it is often acute and may be severe and life-threatening, and serum PTH is suppressed
- ✓ Treatment of severe, symptomatic hypocalcemia—requires intravenous calcium through a central line

Osteoporosis

Osteoporosis is the most common skeletal disorder encountered in clinical practice. It is characterized by decreased bone mass, leading to bone fragility and increased risk of fracture. Bone mineral density can be quantified with dual energy x-ray absorptiometry (DXA). **Osteopenia** is defined as bone mass that is between 1.0 and 2.5 SDs below the mean peak bone mass of a sex-matched control population and is designated by a T score between –1.0 and –2.5. **Osteoporosis** is defined as bone mass of at least 2.5 SDs below the mean peak bone mass of a sex-matched control population and is designated by a T score of –2.5 or less (eg, –3.0, –4.0).

Key Definitions

Osteopenia: *bone mass between 1.0 and 2.5 SDs below mean peak bone mass of a sex-matched control population; T score between –1.0 and –2.5.*

Osteoporosis: *bone mass ≥2.5 SDs below mean peak bone mass of a sex-matched control population; T score ≤–2.5.*

Etiologic Factors

Osteoporosis may be primary or secondary. Primary osteoporosis (postmenopausal osteoporosis and senile osteoporosis, which occurs in older men and women) is more common. Secondary osteoporosis may result from endocrine, nutritional, intestinal, neoplastic, or genetic disorders, use of certain drugs, or physical immobilization (Box 12.2).

Clinical Features

Fractures can occur with minor trauma. Osteoporotic fractures heal normally. Vertebral fractures lead to loss of height and spinal deformity. Serum levels of calcium, phosphate, and alkaline phosphatase are normal (with the exception of acute fracture changes).

Diagnosis

The diagnosis of osteoporosis is based on the finding of low bone mass by DXA (T score ≤–2.5) or the presence of fragility fractures (eg, a fracture that occurred after a fall from standing height). Other causes of low bone mass must be excluded. Osteomalacia may coexist with osteoporosis. Myeloma and metastatic disease should be excluded as causes of pathologic fracture.

Secondary causes of osteoporosis also should be excluded. Evaluation should include serum levels of calcium,

Box 12.2 • Causes of Secondary Osteoporosis

Endocrine: hypogonadism, hyperparathyroidism, hyperthyroidism, hypercortisolism

Nutritional and intestinal tract: calcium deficiency, protein malnutrition, alcoholism, malabsorption, current smoking, primary biliary cirrhosis

Neoplastic disorders: multiple myeloma, leukemia, lymphoma, systemic mastocytosis

Genetic disorders: osteogenesis imperfecta

Culprit drugs: corticosteroids, heparin, anticonvulsants, gonadotropin-releasing hormone analogues (suppress sex steroid production), aromatase inhibitors

25-hydroxyvitamin D, creatinine, thyrotropin, and, for men, testosterone (free, bioavailable, and total). The patient's medication list should be thoroughly reviewed for possible culprit drugs (eg, glucocorticoids), and the threshold should be low for ruling out endogenous Cushing syndrome and multiple myeloma. DXA should be used as a screening study for patients at risk for osteoporosis (eg, women age 65 years and men age 70 years or older, younger women or men with risk factors for osteoporosis or osteoporotic fracture, and men with a fragility fracture).

Prevention and Treatment

Bone loss can be limited through adequate lifestyle activities, including regular weight-bearing exercise, tobacco avoidance, and avoidance of excessive alcohol use. All adults should consume an adequate amount of vitamin D (400-800 international units) and calcium (1,000-1,200 mg) daily.

Pharmacotherapy should be recommended to all patients with a history of fragility fracture or with osteoporosis based on a T score of −2.5 or less. For the decision on whether to initiate pharmacotherapy for patients with osteopenia, one should consider the use of the Fracture Risk Assessment (FRAX) algorithm, a freely available Web-based tool developed by the World Health Organization to quantify the fracture risk for individual patients. FRAX is derived from studies of population-based cohorts in different countries, thereby allowing for a more individualized assessment. It includes known risk factors in a weighted formula and generates a number that represents the probability (a percentage) of a fragility fracture occurring in the next 10 years. In the United States, pharmacotherapy is recommended for patients with osteopenia who have a probability of 20% or more for any major osteoporotic fracture or a probability of 3% or more for a hip fracture.

Therapy requires adequate calcium and vitamin D supplementation, similar to preventive approaches. Bisphosphonates are considered first-line therapy for osteoporosis. Alendronate, risedronate, and ibandronate are oral bisphosphonates with potent antiresorptive effects that prevent bone loss. They reduce fracture risk and are effective in preventing glucocorticoid-induced bone loss. Adverse effects include dyspeptic symptoms and esophagitis, particularly if the medication is taken incorrectly. Ibandronate and zoledronic acid are intravenous bisphosphonates approved for treatment of osteoporosis when oral forms are not tolerated or cannot be administered. Osteonecrosis of the jaw and subtrochanteric fractures are rare complications of bisphosphonate therapy; the risk is significantly higher among patients receiving frequent intravenous bisphosphonate infusions while being treated for a malignancy. Bisphosphonates should not be given to patients who have creatinine clearances of less than 30 to 35 mL/min because of the risk of renal osteodystrophy.

Estrogen replacement is effective for treating osteoporosis in postmenopausal women, yet this approach is not indicated as primary therapy because other therapies are more effective and because estrogen therapy has known risks (breast cancer, venous thrombosis, and cardiovascular disease). Raloxifene is a selective estrogen receptor modulator (SERM) effective in the prevention of both osteoporosis and breast cancer. It is less effective than bisphosphonates and estrogens with regard to bone benefits, and it increases the risk of thrombotic events.

Denosumab is a monoclonal antibody and another potent antiresorptive agent that blocks the action of receptor activator of nuclear factor-κB (RANK) ligand, thus reducing osteoclastogenesis. It is administered intravenously every 6 months, and it can be used in patients with renal insufficiency. The PTH-related analogues (teriparatide and abaloparatide) potently enhance bone formation by increasing bone turnover. Patients who have increased bone turnover (eg, Paget disease) or an increased risk of osteosarcoma (eg, prior radiotherapy to bone) are not candidates for these therapies, which are administered as a daily subcutaneous injection for a maximum of 2 years. Nasal calcitonin is a weak antiresorptive agent with some analgesic properties and is not useful for prolonged therapy. While the best assessment of therapeutic efficacy for each agent is clinical (eg, the absence of additional fractures), demonstration of further decreases in bone mineral density by DXA should prompt a reevaluation of the treatment plan.

Osteomalacia

Definition and Etiologic Factors

Osteomalacia is characterized as inadequate mineralization of newly formed bone. Normal bone mineralization requires adequate calcium and phosphate concentrations, functional osteoblasts, and optimal conditions for the mineralization of mature osteoid. Osteomalacia ensues when these conditions are not met. Vitamin D deficiency is the most common cause of osteomalacia. This deficiency results from inadequate oral intake of vitamin D, malabsorption (eg, celiac disease or following a gastric bypass procedure), limited sun exposure, or decreased liver production of 25-hydroxyvitamin D (due to liver disease or drug adverse effect). Renal disease and inherited disorders affecting activation or action of vitamin D can also cause osteomalacia. Less commonly, phosphate deficiency may result from malnutrition or increased renal losses. This is seen in inherited conditions such as hypophosphatemic rickets. An acquired tubular phosphate leak can occur with some mesenchymal tumors (oncogenic osteomalacia) or in multiple myeloma (generalized tubular defect in renal Fanconi syndrome).

Key Definition

Osteomalacia: *inadequate mineralization of newly formed bone.*

Clinical Features

Typical symptoms of osteomalacia include diffuse bone pain and tenderness along with muscle weakness. Calcium levels

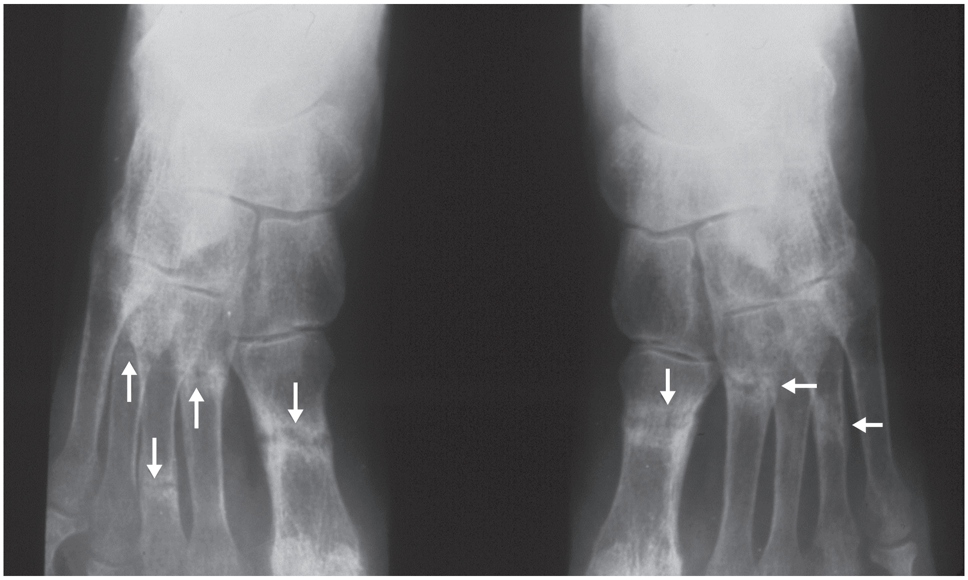


Figure 12.1. *Osteomalacia. Plain radiograph of metatarsal pseudofractures in a patient with osteomalacia shows bilateral, symmetrical, radiolucent lines (arrows) perpendicular to the bone cortex. In general, they are thought to represent either stress fractures repaired with inadequately mineralized osteoid or bone erosions generated by nearby arterial pulsations.*

(Courtesy of Bart L. Clarke, MD, Mayo Clinic, Rochester, Minnesota; used with permission.)

(serum and urinary) and serum phosphorus levels are low or low-normal, and the serum bone alkaline phosphatase level is usually increased. With vitamin D deficiency, secondary hyperparathyroidism also occurs. Radiographs can display fractures or pseudofractures in later stages of osteomalacia (Figure 12.1). Pseudofractures appear as narrow lines of radiolucency perpendicular to the cortical bone surface; they are frequently bilateral and symmetrical. They are found most commonly in the pubic rami and the medial aspect of the femur near the femoral head.

Therapy

Effective therapy for osteomalacia requires treating the underlying disorder and providing adequate calcium and phosphate to the areas of inadequate mineralization. This treatment usually is achieved with calcium, vitamin D, and, when indicated, phosphate supplementation. Vitamin D dosing regimens vary, but a common approach is 50,000 international units weekly for 8 weeks followed by 800 international units daily for maintenance. Osteomalacia is considered adequately treated when urinary calcium excretion and bone mineral density start to increase. The goal of therapy is to achieve bone healing while normalizing the serum concentrations of calcium, phosphate, vitamin D, and alkaline phosphatase. The alkaline phosphatase level can stay elevated for several months after correction of vitamin D deficiency. During therapy, serum and urinary calcium levels should be monitored closely to avoid hypercalcemia, hypercalciuria, and nephrocalcinosis.

Paget Disease

Paget disease affects 3% of the US population older than 45 years and is characterized by increased bone resorption with disorganized bone remodeling. Its pathogenesis is not fully understood.

Clinical Features

Most patients are asymptomatic and present with increased serum levels of alkaline phosphatase or a radiographic abnormality. Serum alkaline phosphatase is the most useful marker of disease activity and response to therapy. When Paget disease is clinically evident, the main clinical features are bone pain and deformity. Disorganized bone remodeling results in decreased tensile strength, skeletal pain, and bone deformities. Pain may also be related to fracture, degenerative changes in adjoining joints, or, rarely, the development of osteosarcoma. Commonly affected sites include the sacrum, spine, femur, tibia, skull, and pelvis. Other complications can include nerve entrapment, hydrocephalus due to the development of platybasia, osteosarcoma, and high-output cardiac failure due to increased vascularity of affected bones.

Diagnosis

Paget disease should be suspected if the serum alkaline phosphatase level is increased and the serum calcium, phosphate, and 25-hydroxyvitamin D levels are normal. A bone scan is the

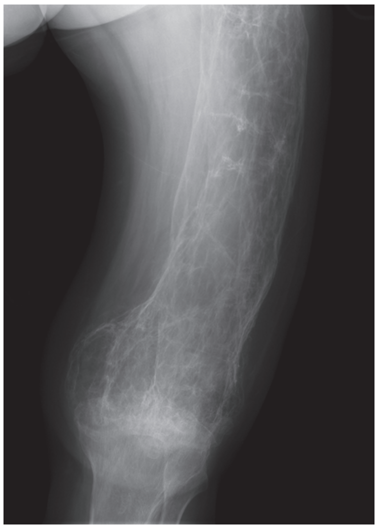


Figure 12.2. *Paget Disease. Plain radiograph of bone involved by Paget disease shows a mixture of sclerotic and lytic lesions with distortion and overgrowth of the involved bone.*

(Courtesy of Bart L. Clarke, MD, Mayo Clinic, Rochester, Minnesota; used with permission.)

most sensitive test for identifying bone lesions of Paget disease. Plain radiographs (Figure 12.2) are best for further definition of the affected bones (expansion, sclerosis, and deformity) and surrounding joints.

Therapy

Many patients require only monitoring of alkaline phosphatase levels. The decision to initiate therapy relates to the presence of symptoms, the location of the bone lesions, and the disease activity. Indications for therapy are bone pain, disease involving bones where complications could occur (skull, spine, weight-bearing bone, or bones near joints), or a marked increase in the serum alkaline phosphatase level. Medical therapy consists of bisphosphonates, most commonly intravenous zoledronic acid. Alkaline phosphatase levels are used to monitor therapy. Orthopedic surgery is rarely needed to treat the deformity, fracture, or degenerative joint disease. Neurosurgical intervention may be required for nerve entrapment syndromes.

KEY FACTS

- ✓ Pharmacotherapy for osteopenia—recommended according to patient's fracture probability: ≥20% probability for any major osteoporotic fracture or ≥3% probability for a hip fracture
- ✓ First-line therapy for osteoporosis—bisphosphonates
- ✓ Most common cause of osteomalacia—nutritional vitamin D deficiency
- ✓ Paget disease—elevated serum bone alkaline phosphatase level with normal serum calcium and vitamin D levels

13

Diabetes Mellitus

EKTA KAPOOR, MBBS; PANKAJ SHAH, MD

Etiologic Factors and Classification

D**iabetes mellitus, characterized** by increased levels of plasma glucose (fasting or postprandial, or both), is the most common metabolic disorder, affecting approximately 10% of the US population.

Type 1 diabetes mellitus (T1D), previously known as *insulin-dependent diabetes mellitus*, is caused by autoimmune destruction of insulin-producing beta cells of the pancreatic islets, resulting in an absolute insulin deficiency. About 10% of diabetic patients have T1D. It usually occurs in children or lean young adults, but T1D can develop at any age. The onset is usually abrupt and dramatic, with symptoms of marked hyperglycemia (polyuria, polydipsia, fatigue, weight loss, and dehydration) or diabetic ketoacidosis (in persons with more severe insulin deficiency). The staging of T1D is stage 1, autoimmunity present, normal glucose level, and normal glucose tolerance; stage 2, autoimmunity with impaired fasting glucose or impaired glucose tolerance; and stage 3, autoimmunity with clinical symptoms and glucose levels in the diabetes range.

A complex interaction between genes and their environment leads to T1D development. T1D is a T-cell–mediated disease, although autoantibodies to islet cells or their products (ie, glutamic acid decarboxylase 65, tyrosine phosphatase IA-2, zinc transporter, and insulin) are frequently present, and they may help to differentiate T1D from the more common type 2 diabetes mellitus (T2D). A "honeymoon" period, marked by restoration of euglycemia, may occur soon after disease onset. However, the duration of this phase is highly variable, and all patients eventually require insulin. Oral agents are not useful in the management of T1D.

T2D, previously known as *non–insulin-dependent diabetes mellitus*, is characterized by beta cell dysfunction (resulting in impaired insulin secretion) and insulin resistance in the target tissues—liver, muscle, and adipose. Genetic factors are thought to be more important in the development of T2D than of T1D. Patients with T2D are typically older and are nearly always overweight or obese. The cases of childhood T2D, however, are increasing with the obesity epidemic in children in the United States. Excess body fat, particularly when concentrated intra-abdominally, leads to insulin resistance, which is the hallmark of T2D. This hallmark involves progressive loss of beta cell function, leading to insulin insufficiency in the physiologic background of insulin resistance. Because of the progressive nature of the disease, most patients with T2D eventually require insulin. Patients with T2D do not have absolute insulin deficiency; therefore, diabetic ketoacidosis (DKA) rarely develops in T2D patients because of their merely skipping diabetes therapy.

Secondary causes of diabetes mellitus include pancreatic disease (pancreatitis, cystic fibrosis, and hemochromatosis), endocrinopathies (Cushing syndrome, pheochromocytoma, and acromegaly), drugs (eg, corticosteroids, tacrolimus) or chemicals, and infections. Certain genetic syndromes are sometimes associated with diabetes (Down syndrome, Klinefelter syndrome, Turner syndrome, and Prader-Willi syndrome).

Gestational diabetes mellitus (GDM) is diabetes first diagnosed in the second or third trimester of pregnancy. By comparison, diabetes diagnosed in the first trimester is *pregestational diabetes*. GDM resolves after child delivery but portends an increased risk of subsequent T2D. When hyperglycemia does not resolve after childbirth, it is believed to be diabetes with onset during pregnancy. The hormonal changes during pregnancy induce a state of insulin resistance, which can lead to hyperglycemia in susceptible women (ie, overweight or obese women with a family history of T2D). Therapy may involve dietary modification, oral medications, or insulin.

Clinical Features

The onset of T1D is usually rapid, with weight loss, polyuria, and polydipsia due to an abrupt, severe insulin deficiency. The manifestation is often precipitated by an infection or another severe physical stress. For about 30% of children and adolescents (ie, persons younger than 20 years), T1D presents with DKA.

T2D usually has a more insidious onset than T1D and is often diagnosed during routine laboratory testing that identifies glucosuria or hyperglycemia. Patients may report blurry vision, nearsightedness, recurrent skin infections, or candidal vaginitis (women) or balanitis (men). Patients sometimes present with chronic diabetic complications (eg, neuropathy, nephropathy, retinopathy, vascular disease) before the recognition of hyperglycemia. Polyuria, polydipsia, and polyphagia may develop only at times of increased insulin resistance (eg, pregnancy, infection, corticosteroid use). Patients occasionally present with hyperosmolar nonketotic coma.

KEY FACTS

- ✓ Cause of T1D—
    - autoimmune destruction of insulin-producing beta cells of the pancreatic islets, resulting in an absolute deficiency of insulin
    - autoantibodies to islet cells or to their products are frequently present
- ✓ Development of T2D—
    - genetic factors are more important than in T1D
    - patients are usually older than patients with T1D
    - patients are nearly always overweight or obese
- ✓ Onset of T1D—usually rapid, with weight loss, polyuria, and polydipsia due to an abrupt, severe insulin deficiency
- ✓ Onset of T2D—more insidious than onset of T1D and often diagnosed during routine laboratory testing that identifies glucosuria or hyperglycemia

Diagnosis

Diabetes mellitus is diagnosed through elevated plasma glucose or hemoglobin A$_{1c}$ (HbA$_{1c}$) levels (Box 13.1). A glucose tolerance test is not required for the diagnosis. Fasting plasma glucose concentration less than 100 mg/dL and HbA$_{1c}$ less than 5.7% are the reference ranges for persons without diabetes mellitus.

Key Definition

Prediabetes: *fasting glucose values of 100-125 mg/dL.*

Box 13.1 • Diagnosis of Diabetes Mellitus and Prediabetes

Criteria for diagnosis of diabetes mellitus

- Casual plasma glucose ≥200 mg/dL in the presence of classic symptoms of hyperglycemia[a]
- Fasting plasma glucose[b] ≥126 mg/dL[c]
- Plasma glucose ≥200 mg/dL 2 h after a 75-g oral glucose load[c]
- HbA$_{1c}$ ≥6.5%[c]

Criteria for diagnosis of prediabetes

- HbA$_{1c}$ 5.7%-6.4%
- Fasting plasma glucose 100-125 mg/dL (impaired fasting glucose)
- Plasma glucose 140-199 mg/dL 2 h after a 75-g oral glucose load (impaired glucose tolerance)

Abbreviation: HbA$_{1c}$, hemoglobin A$_{1c}$.

[a] Polyuria, polydipsia, and unexplained weight loss.

[b] No calorie intake for 8 h.

[c] In the absence of symptoms of hyperglycemia, the results should be confirmed by repeat testing.

The diagnosis of GDM requires an oral glucose tolerance test (OGTT) (see the Diabetes and Pregnancy section).

Therapy for T1D

Insulin replacement is necessary for treatment of T1D; oral agents are not useful in its management. Therapy is aimed at preventing acute and chronic complications of diabetes mellitus while allowing the patient to maintain a healthy and active lifestyle with optimal glycemic control and minimal hypoglycemia. Intensive insulin therapy requires considerable commitment from the patient to self-monitor plasma glucose concentrations and adjust insulin doses accordingly. Intensive therapy with tight glycemic control prevents or markedly decreases the risks of chronic micro- and macrovascular complications of diabetes and reduces the mortality rate.

The amylin analogue, pramlintide, can be added to insulin therapy to manage hyperglycemia of T1D. In persons with T1D, pramlintide use has been associated with severe hypoglycemia. Therefore, the mealtime insulin dose is decreased by 50% when adding pramlintide therapy for patients with T1D.

Nutrition

People with diabetes have no single ideal dietary distribution of calories among carbohydrates, fats, and proteins. The American Diabetes Association opines that macronutrient distribution should be individualized while keeping total calorie and metabolic goals in mind. Intake should allow for maintenance of a healthy weight and for a match of the meal insulin doses to the meal carbohydrate content. In some diabetes cases, the fat and protein intake is also taken into consideration to determine mealtime insulin dosing. Patients are advised to maintain a diet consistent with the content of the major food groups or to adjust the insulin dose according to their intake of carbohydrate (and sometimes protein and fat) at each meal.

Exercise

The glycemic response to exercise depends on the glucose level before exercise, the duration and type of exercise, the patient's physical fitness, and the relation of exercise to meals and insulin injections. Glucose levels should be monitored before and after exercise. If strenuous anaerobic exercise is initiated while the patient is hyperglycemic, the serum glucose concentration may increase further. Patients should always carry appropriate identification and have access to sugar.

Insulin Therapy

Intensive insulin therapy attempts to mimic the insulin secretion of a healthy pancreas. Once- or twice-daily long-acting insulin (eg, degludec, detemir, glargine) provides the basal insulin needs and short (regular) or rapid-acting insulin (eg, lispro, aspart, glulisine) is injected at mealtimes to provide the prandial needs.

A subcutaneous insulin infusion pump can provide programmable continuous insulin infusion or an insulin bolus required to correct high glucose or meet the needs for the meals. A pump used with a glucose sensor can temporarily autosuspend the delivery of insulin when glucose is low. Newer systems can adjust the "basal" insulin infusion rates on the basis of continuously monitored interstitial glucose with a sensor. Pumps allow the patients to temporarily change the infusion rate of basal insulin—for example, during exercise.

Typically, therapy for patients with T1D is started at an insulin dose between 0.25 to 0.3 U/kg/day. The ultimate insulin needs for a typical patient with T1D are approximately 0.5 to 1.0 U/kg/day. Insulin requirements may increase markedly during illness.

Glycemic Goals of Optimal Therapy

The target preprandial plasma glucose level is 80 to 130 mg/dL to achieve an HbA_{1c} less than 7.0%. Higher target levels are recommended for children, adolescents, older patients with comorbidities and limited life expectancy, and patients at risk for hypoglycemia who have a limited ability to recognize it. For women with T1D who are considering pregnancy, tight glucose control (HbA_{1c} often <6.5%) starting weeks to months before pregnancy is critical to decrease the risk of birth defects. Tight glycemic control (HbA_{1c} 6.0%-6.5%) during pregnancy prevents macrosomia and other maternal and fetal complications.

Monitoring

Glucose concentration should be self-monitored 4 times daily—before meals and at bedtime. If the patient has unexplained morning hypoglycemia or hyperglycemia, blood glucose should be measured between 2 AM and 4 AM. HbA_{1c} should be measured every 3 months. A continuous glucose-monitoring sensor can alert patients of a low level, high level, and rapid change in glucose concentrations. Sensor data can be used to adjust the insulin dose.

Therapy for T2D

Most patients with T2D are obese, have a sedentary lifestyle, and often have multiple cardiovascular risk factors, such as hypertension and dyslipidemia. Therapy should include modification of risk factors (including exercise, weight loss, and improved nutrition) and achievement of appropriate glycemic control with a near-normal HbA_{1c} level in the absence of hypoglycemia.

A goal of losing 5% to 10% of initial body weight is recommended for patients with body mass index (BMI) values greater than 25 (calculated as weight in kilograms divided by height in meters squared). Exercise improves insulin action, facilitates weight loss, increases a sense of well-being, and reduces cardiovascular risks (increases high-density lipoprotein cholesterol [HDL-C] and decreases very low-density lipoprotein [VLDL] and triglycerides). Exercise recommendations should be modified appropriately for patients with preexisting coronary or peripheral vascular disease.

Drug Therapy for T2D

Metformin

Metformin is the first-line agent for managing T2D. Unless a contraindication for its use exists, all patients receiving pharmacotherapy for T2D should receive metformin. Its most important action is suppression of hepatic glucose production. It also enhances the sensitivity of peripheral tissues (muscle and adipose) to insulin. Metformin is effective as monotherapy and in combination therapy with other glucose-lowering drugs. It lowers HbA_{1c} by 1% to 2%.The main adverse effect is diarrhea, which can be minimized by taking metformin with meals. Patients taking metformin do not usually gain weight and may even lose some weight. Metformin may improve lipid levels and lower the risk of adverse vascular outcomes and death. The drug may lead to vitamin B_{12} deficiency due to decreased absorption. Generally, metformin should be withheld when a patient is hospitalized. The risk of lactic acidosis is a concern, but the condition is rare. Nevertheless, given the high fatality rate of patients with lactic acidosis, metformin is contraindicated in several situations, including renal impairment, decompensated heart failure, severe infection, and liver disease (Box 13.2).

Sulfonylureas

Sulfonylureas (eg, glyburide, glipizide, glimepiride) are insulin secretagogues. Their efficacy depends on the presence of adequate beta cell function. They lower HbA_{1c} by 1% to 2%. Despite the advantage of low cost, sulfonylureas have fallen out of favor because of hypoglycemia risk, risk of weight gain, and

Box 13.2 • Considerations of Metformin Use

Contraindications
- Severe renal impairment (eGFR <30 mL/min/1.73 m^2)
- Known hypersensitivity to metformin
- Acute or chronic metabolic acidosis, including diabetic acidosis

Precautions, including risk factors for metformin-associated lactic acidosis
- Renal impairment (eGFR 30-45 mL/min/1.73 m^2)
- Use of iodinated radiocontrast medium[a]
  - for arterial studies
  - in people with eGFR of 30-60 mL/min/1.73 m^2
  - in people with hepatic impairment, alcoholism, or heart failure
- Hypoxic procedures[a] or states
- Excessive alcohol intake
- Hepatic impairment

Abbreviation: eGFR, estimated glomerular filtration ratio.

[a] Discontinue metformin therapy before the procedure. Reevaluate eGFR at 48 h after the procedure and restart metformin use if no contraindications are present.

perhaps increased cardiovascular risk (especially with glyburide). Sulfonylureas should be used with caution when patients have advanced hepatic or renal disease. The risk of hypoglycemia from sulfonylurea use is higher with longer-acting sulfonylureas (eg, glyburide), in older patients, and with renal failure.

Meglitinides

Similar to sulfonylureas, meglitinides (eg, repaglinide, nateglinide) also stimulate insulin release. They have extremely short half-lives and are taken before each meal to target postprandial glycemic excursions. Concerns with their use include hypoglycemia (although rarely severe) and weight gain.

Thiazolidinediones

Thiazolidinediones (eg, rosiglitazone, pioglitazone) enhance peripheral insulin sensitivity by activating peroxisome proliferator-activated receptor-γ. They do not cause hypoglycemia, and they lower the HbA_{1c} by 1% to 2%. Pioglitazone causes marked fluid retention, thereby increasing the risk of heart failure, and should not be prescribed for patients who have congestive heart failure. Substantial weight gain and osteoporosis have been reported with thiazolidinedione use.

α-Glucosidase Inhibitors

α-Glucosidase inhibitors (eg, acarbose, miglitol) inhibit upper intestinal tract glucosidases, limiting the conversion of complex carbohydrates to monosaccharides. Modest efficacy (eg, decrease in HbA_{1c} by less than 1%) and serious gastrointestinal tract adverse effects (eg, flatulence in 70% of users) limit their clinical use. Glucose is necessary to treat hypoglycemia in patients taking an α-glucosidase inhibitor.

Dipeptidyl-peptidase-4 Inhibitors

Dipeptidyl-peptidase-4 (DPP4) inhibitors (eg, sitagliptin, saxagliptin, linaglitptin, alogliptin) potentiate the effect of endogenous glucagon-like peptide-1 (GLP1) through inhibiting its degradation by DPP4. Glucose lowering occurs through enhancing GLP1-mediated insulin secretion. DPP4 inhibitors do not have a strong effect on gastric emptying or food intake and do not affect a patient's weight. They do not cause hypoglycemia. Recent reports suggest that DPP4 inhibitor use is associated with new-onset or relapse of inflammatory arthritis.

GLP1 Analogues

Injections of GLP1 analogues (eg, exenatide, liraglutide, albiglutide, dulaglutide, lixisenatide) augment insulin secretion and glucagon suppression in response to glucose. They also slow gastric emptying, reduce appetite, and lead to moderate weight loss. Nausea and vomiting occur in a substantial proportion of patients early in therapy, but the symptoms often subside. Used in combination with sulfonylurea, these agents can lead to hypoglycemia. Liraglutide has US Food and Drug Administration (FDA) approval to reduce the risk of major adverse cardiovascular events in adults with T2D and established cardiovascular disease.

GLP1 analogues are resistant to DPP4 and therefore are not used in combination with DPP4 inhibitors.

Sodium Glucose Cotransporter-2 Inhibitors

Sodium glucose cotransporter-2 (SGLT2) inhibitors (eg, canagliflozin, dapagliflozin, empagliflozin) prevent glucose reabsorption from the proximal convoluted tubules, thereby reducing the renal glucose threshold and the risk of glycosuria and improving the plasma glucose. SGLT2 inhibitors cause polyuria, polydipsia, vulvovaginitis, balanitis, and dehydration. They also can cause hyperkalemia, DKA (without severe hyperglycemia), and increased risk of amputation. Empagliflozin has been approved by the FDA to reduce the risk of cardiovascular death in adult patients who have both T2D and cardiovascular disease.

Insulin

Insulin is often reserved for 1) patients with T2D when diet and oral agents (monotherapy and combination therapy) provide inadequate glycemic control, 2) sick patients or patients with advanced hepatic or renal disease when oral agents may be contraindicated, 3) patients who require rapid glycemic control, and 4) patients who are pregnant, under perioperative care, or severely ill. Patients with T2D often have some degree of meal-stimulated endogenous insulin secretion, which allows treatment with simpler insulin regimens than for T1D. Once-daily injections of intermediate-acting insulin taken at bedtime, in combination with a noninsulin agent or twice-daily injections of intermediate-acting insulin (morning and bedtime), are commonly used to manage T2D. Insulin therapy is associated with some degree of weight gain for most patients. Insulin is often combined with most other antidiabetic agents, although sulfonylurea is often discontinued. When intermediate or basal insulin therapy (with other agents) is unable to achieve glycemic goals, a patient's treatment can be changed to a more intensive insulin therapy (basal-bolus regimen), to a combination of basal insulin with a GLP1 analogue, or to the split-mix (or premixed) insulin regimen scheduled with meals.

An amylin analogue, pramlintide, is also approved by the FDA for T2D patients receiving insulin therapy. Amylin is a peptide that the beta cells co-secrete with insulin. Pramlintide injection lowers glucose levels by delaying gastric emptying, suppressing postprandial glucagon secretion, and decreasing appetite. Its effect in lowering blood glucose concentration is complementary to that of insulin. It can cause nausea, but hypoglycemia is not common in T2D; by comparison, it is used at a much higher dose in T2D than in T1D. Pramlintide therapy does not cause weight gain and may even lead to some weight loss.

KEY FACTS

✓ Therapy for T1D—

- amylin analogue pramlintide can be used to manage both T1D and insulin-requiring T2D
- insulin dosage for a typical patient (within 20% of ideal body weight and without intercurrent illness) is 0.5-1.0 U/kg daily
- target preprandial plasma glucose level is 90-130 mg/dL
- HbA_{1c} target is <7.0%

✓ Therapy for T2D—

- metformin: first-line agent for all patients who are receiving pharmacotherapy and have no contraindications; may lead to vitamin B_{12} deficiency (from decreased absorption)
- sulfonylureas: risk of hypoglycemia, risk of weight gain, and perhaps increased cardiovascular risk
- thiazolidinediones: pioglitazone should not be prescribed for patients who have congestive heart failure (causes marked fluid retention)
- α-glucosidase inhibitors: limited clinical use because of modest efficacy (lowers HbA_{1c} by <1%) and gastrointestinal tract adverse effects (flatulence)
- GLP1: nausea and vomiting may occur early in therapy but often subside
- insulin: regimens are simpler than for patients with T1D (often patients with T2D have meal-stimulated endogenous insulin secretion)

Hypoglycemia in Diabetes

In persons with diabetes, hypoglycemia is caused by insulin and sulfonylurea; less frequently, it is caused by meglitinides, by SGLT2 inhibitors, and by GLP1-based therapies when combined with insulin or sulfonylureas. A glucose concentration of 70 mg/dL or less is considered an alert level (level 1), and a concentration less than 54 mg/dL is considered clinically significant hypoglycemia (level 2). Severe hypoglycemia (level 3) is defined as an event associated with severe cognitive impairment requiring external assistance for recovery.

Hypoglycemia may result from unplanned exercise, inappropriate dosing of insulin, or inadequate carbohydrate intake. Patients with long-standing T1D may not have adrenergic symptoms of hypoglycemia before they have neurologic symptoms (*hypoglycemia unawareness*) due to repeated events of neuroglycopenia. Prevention of hypoglycemia has been shown to reverse or ameliorate hypoglycemia unawareness in some patients. Hypoglycemia can occur at night (*nocturnal hypoglycemia*) and may not be apparent if glucose is checked at bedtime and at breakfast. Patients may report symptoms such as nightmares, morning headache, or night sweats. Periodic monitoring of blood glucose between 1 AM and 3 AM is essential, especially if the patient takes intermediate insulin in the evening. Preventive strategies include increasing the bedtime snack or modifying the insulin regimen.

Among patients with long-standing T1D, inability to secrete glucagon leads to defective counterregulation, and patients become dependent on the autonomic nervous system to respond to hypoglycemia. The use of β-blockers in these situations can abolish the warning palpitations that are caused by hypoglycemia.

Lower doses of insulin may be needed for patients with renal impairment. Alcohol may interfere with gluconeogenesis and the perception of hypoglycemic symptoms. Hypoglycemia also may be a manifestation of cortisol deficiency (eg, Addison disease, autoimmune hypophysitis).

Continuous glucose-monitoring sensors can be useful to identify episodes or expected episodes of hypoglycemia and warn the patient to action. Some insulin pumps automatically pause if the patient does not respond to the alarm of a low glucose level.

Acute Complications of Diabetes Mellitus

Acute hyperglycemic complications of diabetes mellitus can be precipitated by absence of insulin or a concurrent illness, or both. Alternatively, acute hyperglycemia can precipitate vascular complications. In addition to dealing with the acute hyperglycemic state, the clinician needs to address the concurrent illness.

Diabetic Ketoacidosis

DKA may be the initial presentation of T1D. Rarely, DKA occurs in persons who have T2D and a major intercurrent illness, including infection, myocardial infarction, or other major stress.

DKA results from a profound insulin deficiency and an excess of counterregulatory hormones such as glucagon. Thus, it may be caused by a failure to take insulin or to increase the insulin dose when the need is increased in times of major stress. The major manifestations of DKA are the direct result of severe insulin deficiency: hyperglycemia, ketosis (due to unrestrained lipolysis and conversion of fatty acids to ketone bodies), and severe dehydration (due to osmotic diuresis). The ketoacids cause an anion gap metabolic acidosis. Patients with DKA may have severe volume contraction.

Diagnosis

Patients usually present with polyuria, polydipsia, poor appetite, nausea and vomiting, abdominal pain, tachypnea, mental obtundation, and coma. Physical findings include evidence of dehydration, decreased mentation, deep and rapid Kussmaul respiration, and a characteristic breath odor (the fruity odor of acetone).

The diagnosis is based on the presence of moderate to severe hyperglycemia (plasma glucose >250 mg/dL), ketonemia (β-hydroxybutyrate >3.0 mmol/L), and an anion gap metabolic acidosis. Associated biochemical abnormalities include hyponatremia, azotemia, and hyperamylasemia. Large body losses of electrolytes occur, but serum levels of potassium, phosphate, and magnesium are often within the reference range or even elevated. Their concentrations often decrease precipitously as the acidosis is corrected.

Treatment

Treatment of DKA requires administration of fluids and insulin to correct the metabolic acidosis and dehydration. Electrolyte levels should be carefully monitored and corrected and the precipitating factors ameliorated. The average fluid deficit in adults is 5 to 8 L. The risk of cerebral edema is decreased through careful rehydration and correction of ketoacidosis, thereby avoiding a rapid decrease in serum osmolality.

Insulin bolus is required if the infusion rate is less than 0.15 unit/kg/hour. Intravenous insulin infusion is usually continued until the ketonemia and anion gap acidosis resolve and the subcutaneous long-acting insulin starts working. The preferred initial fluid is 0.9% saline because it can expand intravascular volume. However, when plasma volume is restored, the fluid can be changed to 0.45% saline with 5% dextrose. Dextrose and insulin infusion is modified to maintain glucose between 150 and 250 mg/dL until the time when the ketonemia clears up.

The potassium deficit is typically 300 to 500 mmol, reflecting low total body stores. Serum potassium levels decrease with correction of the acidosis. Potassium should be added to the intravenous fluids as soon as renal perfusion and urine flow are ensured. Phosphate repletion is indicated at a phosphate level less than 1 mg/dL. The serum phosphate level must be monitored carefully, owing to the risk of hypocalcemia, seizures, and death with hypophosphatemia.

DKA is a life-threatening condition. Most deaths result from cerebral edema, which carries a mortality rate of more than 20%. Other complications of DKA include myocardial infarction, acute respiratory distress syndrome, stroke, deep vein thrombosis and pulmonary embolism, and arrhythmias. After successful therapy, the goal is to avoid recurrence through education of the patient.

Hyperglycemic Hyperosmolar State

Hyperglycemic hyperosmolar state is characterized by hyperglycemia (more profound than the hyperglycemia in DKA) and hyperosmolar dehydration *without* ketoacidosis. This typically occurs in poorly treated T2D when insulin levels are sufficient to inhibit excess lipolysis and ketogenesis but not to suppress hyperglycemia. High concentrations of urinary glucose provoke an osmotic diuresis, resulting in marked dehydration and decreased renal function. It is commonly precipitated by an acute illness, such as myocardial infarction, pancreatitis, infection, or surgery.

Diagnosis

Hyperglycemic hyperosmolar state should be suspected in any patient with diabetes who presents with an altered level of consciousness and severe dehydration. Laboratory abnormalities include hyperglycemia (blood glucose often >600 mg/dL), absence of serious elevations of ketone levels, and plasma hyperosmolality (>320 mOsm/kg).

Treatment

The objectives of treatment are to restore volume and osmolality and to control the hyperglycemia. Total fluid loss is often larger in hyperglycemic hyperosmolar nonketotic coma than in DKA. Fluid resuscitation and insulin infusion are necessary. Renal failure can complicate electrolyte replacement. Repeated neurologic evaluation is essential because focal deficits or seizures may become apparent during therapy.

Complications include vascular events such as myocardial infarction or stroke, cerebral edema, and hypokalemia. The mortality rate can be up to 50%.

Chronic Complications of Diabetes Mellitus

Microvascular Disease in Diabetes

The microcirculation is damaged by chronic hyperglycemia, hypertension, and other metabolic abnormalities associated with diabetes. Clinical manifestations include retinopathy, nephropathy, and neuropathy. Diabetic retinopathy is present in 15% to 20% of patients when T2D is diagnosed and in 50% of patients by 15 years after the diagnosis. At the least, the early phase of diabetic retinopathy occurs in most patients with T1D within 10 years after diagnosis. Patients usually undergo a dilated ophthalmic examination annually. If the dilated examination has been normal for 2 years, retinal photography can be used instead, and the frequency of monitoring can be reduced. Background diabetic retinopathy is characterized by microaneurysms, hard exudates, hemorrhages, and macular edema. Retinal ischemia leads to proliferative retinopathy, stimulating the growth of new vessels that are fragile and prone to hemorrhage; loss of vision may result. For blindness prevention, proliferative retinopathy is treated with panretinal or focused laser photocoagulation or intraocular injections of vascular endothelial growth factor inhibitors. Treatment of hypertension, hyperglycemia, glaucoma, and dyslipidemia is also important.

Screening for diabetic kidney disease involves measurement of serum creatinine and the urinary albumin to creatinine ratio. Good glucose control, smoking cessation, and blood pressure control help prevent onset and progression of diabetic kidney disease. In the presence of increased urinary albumin excretion or hypertension, the first-line therapy is either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker. These 2 agents are never combined, although treatment with any of them often needs to be combined with thiazide-like diuretics or dihydropyridine calcium channel blockers. ACE inhibitors or angiotensin receptor blockers are not indicated in the absence of increased urinary albumin excretion or hypertension for so-called renal protection.

Infections and Diabetes

Bacterial and fungal infections occur more frequently in people with poorly controlled diabetes. These infections include carbuncles (*Staphylococcus aureus*), malignant external otitis (*Pseudomonas*), and in DKA, rhinocerebral mucormycosis (*Mucor* species). Candidiasis and furunculosis also occur more frequently with poorly controlled diabetes.

Atherosclerotic Vascular Disease in Diabetes

Ischemic cardiovascular disease appears earlier and is more extensive in diabetic persons than in the general population. Coronary heart disease accounts for the majority of deaths among persons with diabetes, and sudden cardiac death may occur. Patients with ischemic heart disease may present with atypical symptoms; angina may manifest as epigastric distress, heartburn, and neck or jaw pain. Myocardial infarction may be silent, and patients may present with sudden onset of left ventricular failure. Patients with diabetes have a higher risk of cerebrovascular and peripheral arterial diseases, but screening for vascular disease has no role in asymptomatic patients.

Hyperlipidemia in Diabetes

In poorly controlled T2D, the concentrations of triglyceride-rich lipoproteins are increased, owing to VLDL overproduction and decreased lipoprotein lipase activity. HDL-C levels are low, and control of glucose and triglyceride levels leads to concentrations that are improved but usually not normalized. Compositional changes in low-density lipoprotein (LDL) (ie, small, dense LDL) that increase the atherogenicity of these particles are more likely to occur in patients with T2D. Statin therapy in a moderate to high dose is indicated for persons with diabetes who are age 40 to 75 years unless they have an LDL cholesterol concentration less than 70 mg/dL.

Diabetes Mellitus in Pregnancy

Pregnancy is a diabetogenic state due to the insulin resistance conferred by various placental hormones, including growth hormone, human placental lactogen, progesterone, and corticotropin-releasing hormone. Women with preexisting diabetes may have worsening diabetic control during pregnancy. Inadequate glycemic control at conception and early in pregnancy increases the risk of congenital malformations; poor glycemic control in late pregnancy increases the risk of macrosomia, and neonatal hypoglycemia, hypocalcemia, polycythemia, hyperbilirubinemia, and respiratory distress. Pregnancy may exacerbate diabetic retinopathy, and nephropathy may lead to pregnancy-induced hypertension and toxemia.

GDM complicates 6% to 7% of all pregnancies, but the rate varies substantially between different racial/ethnic groups. Women at high risk for GDM include obese women, women who belong to a high-risk racial/ethnic group, and women with glycosuria, a personal history of GDM, a previous adverse obstetric outcome, or a family history of T2D. These women should undergo screening for diabetes at the first prenatal visit. Most other women should undergo screening at 24 to 28 weeks of gestation. Women of normal weight who are younger than 25 years are excluded from this recommendation because their risk of GDM is low. The screening test is a 50-g oral glucose challenge test. A plasma glucose level of 140 mg/dL or more at 1 hour after ingestion of the glucose load is considered a positive result and should prompt formal testing with a 100-g OGTT. GDM is diagnosed if 2 or more of the plasma glucose values are abnormal during the OGTT (ie, fasting glucose >105 mg/dL; 1-hour glucose >190 mg/dL; 2-hour glucose >165 mg/dL; or 3-hour glucose >145 mg/dL).

Treatment

Home monitoring for blood glucose and urine ketones is important for women with GDM. Postprandial glucose concentrations are closely associated with macrosomia and neonatal complications, and they therefore are often used to guide therapy. The fasting blood glucose concentration should be 95 mg/dL or less; 1-hour postprandial level, 140 mg/dL or less; and 2-hour postprandial goal, 120 mg/dL or less.

Women with GDM should be tested with the OGTT between 4 and 12 weeks postpartum to ensure normalization of glucose. However, they continue to be at a high risk for T2D, should be encouraged to institute lifestyle changes to prevent onset of T2D, and should be evaluated periodically.

Hypoglycemia in Nondiabetic Patients

Etiologic Factors

Hypoglycemic disorders may be classified as *insulin mediated* and *noninsulin mediated*. Causes of insulin-mediated hypoglycemia include insulinoma, sulfonylurea or exogenous insulin use, and autoimmune hypoglycemia mediated by insulin antibodies that bind insulin and unpredictably release it, causing hypoglycemia or activating antibodies to insulin receptors and thereby directly causing hypoglycemia. Noninsulin-mediated hypoglycemia may be related to drugs, alcohol use, or cortisol insufficiency. Renal failure, liver failure, and sepsis are common causes of noninsulin-mediated hypoglycemia in hospitalized patients. Tumors that produce insulinlike growth factor 2, such as mesenchymal or epithelial tumors, may also cause hypoglycemia.

Clinical Features

Hypoglycemia may cause hyperadrenergic symptoms (palpitations, sweating, tremor, and nervousness) and neuroglycopenic symptoms (confusion, inappropriate affect, blurred vision, diplopia, seizures, and loss of consciousness). Symptoms are relieved promptly after oral carbohydrate intake.

Diagnosis

The symptoms due to hypoglycemia are nonspecific, so their presence alone does not establish hypoglycemia as the cause. The Whipple triad must be present for a diagnosis of hypoglycemia. These are symptoms of hypoglycemia, presence of low plasma glucose level during symptoms (*not* measured with fingerstick glucose testing), and reversal of symptoms with normalization of plasma glucose.

Insulinoma

Insulinoma is an insulin-secreting islet cell tumor that usually causes fasting hypoglycemia. It is diagnosed when plasma glucose is low (often <50 mg/dL) with inappropriately normal or increased plasma insulin and C-peptide concentrations in the absence of insulin secretagogues (sulfonylurea or meglitinides). If a blood sample cannot be drawn during 1 of the episodes, a 72-hour fasting protocol is often required to induce hypoglycemia for diagnostic biochemical testing. Ultrasonography (transabdominal and endoscopic), computed tomography, and magnetic resonance imaging of the pancreas are used to identify most insulinomas. When imaging is not conclusive, selective pancreatic arterial calcium stimulation of insulin release can help regionalize the area of insulin overproduction. The means to successful removal is surgical exploration of the pancreas by an experienced surgeon in combination with intraoperative ultrasonography. Almost all insulinomas can be identified and excised in this manner. Patients with insulinoma who decline surgical excision or who have persistent or recurrent malignant insulinoma may be treated with intratumor alcohol injection or oral diazoxide. Diazoxide inhibits insulin secretion, but adverse effects—edema and malaise—limit its tolerability.

Key Definition

Insulinoma: *insulin-secreting islet cell tumor that usually causes fasting hypoglycemia.*

KEY FACTS

✓ DKA—
  - rare in patients with T2D
  - major manifestations (from severe insulin deficiency) are hyperglycemia, ketosis, and severe dehydration
  - ketoacids cause an anion gap metabolic acidosis

✓ Treatment of DKA—fluids and insulin to correct metabolic acidosis and dehydration

✓ Hyperglycemic hyperosmolar nonketotic coma—
  - hyperglycemia (more profound than in DKA)
  - hyperosmolar dehydration *without* ketoacidosis

✓ GDM—
  - risk factors for pregnant women are obesity, glycosuria, member of a high-risk racial/ethnic group, personal history of GDM or a previous adverse obstetric outcome, or family history of T2D
  - screening for pregnant women at high risk should occur at first prenatal visit
  - screening for other pregnant women should occur at 24-28 weeks of gestation

✓ Whipple triad for diagnosis of hypoglycemia—
  - symptoms of hypoglycemia
  - low plasma glucose level during symptoms
  - reversal of symptoms with glucose administration

✓ Insulinoma diagnostic criteria—
  - plasma insulin ≥3 mcIU/mL
  - C-peptide ≥0.6 ng/mL when plasma glucose <50 mg/dL and plasma sulfonylurea is undetectable

Postprandial Hypoglycemia

Postprandial symptoms are not always caused by postprandial hypoglycemia. **Postprandial hypoglycemia** is defined as symptomatic hypoglycemia occurring within 4 hours after a meal. Patients can have postprandial symptoms and even hypoglycemia after gastrointestinal surgical procedures (such as gastric bypass) due to dumping syndrome.

Key Definition

Postprandial hypoglycemia: *symptomatic hypoglycemia occurring within 4 hours after a meal.*

Therapy

Treatment of hypoglycemia is directed at correction of both the hypoglycemia and its underlying cause. For patients with serious hypoglycemia who cannot eat or drink, 1 mg glucagon can be administered to stimulate endogenous glucose production. Alternatively, intravenous dextrose can be given, although this treatment may be associated with superficial phlebitis and pain.

14

Gonadal and Adrenal Disorders

PANKAJ SHAH, MD

Disorders of the Adrenal Glands

Adrenocortical Failure

Etiologic Factors

Clinically relevant adrenocortical deficiencies may involve cortisol or aldosterone, or both, as a consequence of adrenocortical disease (primary failure and often both) or tropic hormone loss (secondary failure and usually only one).

Primary Adrenocortical Failure (Addison Disease)

Patients with primary adrenocortical failure usually present because of the lack of both aldosterone and cortisol. This lack may be due to organ-specific autoimmunity, granulomatous adrenalitis (eg, tuberculosis, histoplasmosis), bilateral adrenal hemorrhage (eg, anticoagulant use, trauma, sepsis [particularly meningococcemia]), congenital adrenal enzyme deficiency, AIDS (rarely), bilateral metastatic malignancies, drug use (such as ketoconazole, which blocks steroidogenesis; rifampin and phenytoin, which accelerate cortisol clearance when cortisol synthesis is already compromised), or immune checkpoint inhibitors (which cause adrenalitis). In the United States, the most common causes are autoimmune adrenalitis and bilateral adrenal hemorrhage.

Secondary Adrenocortical Failure

Secondary cortisol deficiency is due to a lack of corticotropin (ACTH). Therefore, it does not affect aldosterone secretion.

Functional central ACTH deficiency, the most common cause of a lack of ACTH, occurs after withdrawal of a prolonged (>3 weeks) use of glucocorticoids in pharmacologic doses (>5 mg prednisone or equivalent).

Structural problems in the hypothalamic-pituitary region may cause isolated ACTH deficiency or, more commonly, may initiate it in association with other characteristics of hypopituitarism. Causes include pituitary tumors, hypothalamic or extrasellar disease, surgery or radiotherapy to the hypothalamic-pituitary region, autoimmune hypophysitis, drug-induced hypophysitis (by immune checkpoint inhibitors), or head injury.

Hypoaldosteronism can occur independently of cortisol deficiency. It may result from a primary disorder of the zona glomerulosa, or it may be secondary to angiotensin II deficiency, which may be a consequence of decreased renal renin release.

Clinical Features

The clinical features of adrenocortical failure depend on the magnitude of the hormone deficiency, whether the failure is partial or complete, whether 1 or all hormones are involved, the rapidity of development of the deficiency, and, when present, changes in the levels of circulating ACTH. The usual manifestation of adrenocortical failure is that of a chronic, slowly evolving disorder (Box 14.1).

Acute Adrenocortical Failure or Adrenal Crisis

Adrenal crisis is suspected in the presence of dehydration, hypotension, or shock with or without concurrent illness; nausea and vomiting, with a history of severe anorexia and weight loss; abdominal pain (may mimic acute abdomen); unexplained fever; and hyponatremia, hyperkalemia, azotemia, hypercalcemia, eosinophilia, and hypoglycemia.

Diagnosis

Endocrine Diagnosis

The symptoms and signs of adrenocortical failure are variable and nonspecific, and diagnosis requires a high degree of clinical suspicion. Blood samples for plasma cortisol and ACTH testing should be drawn before presumptive therapy for glucocorticoid insufficiency is begun.

The reference range for morning serum cortisol is 7 to 27 mcg/dL. In the absence of synthetic glucocorticoids, a value less than 3 mcg/dL strongly indicates adrenocortical failure; between

Box 14.1 • Manifestations of Adrenocortical Failure

Cortisol deficiency: severe malaise, fatigue, and decreased vitality, energy, and stamina; muscle weakness; anorexia, weight loss; abdominal pain, nausea, vomiting, or diarrhea (may mimic abdominal malignancy); mood and behavior changes; headaches; hyponatremia, fasting hypoglycemia, transient hypercalcemia, anemia, lymphocytosis, and eosinophilia. *Associated other autoimmunity*: Vitiligo, thyroid autoimmunity

Aldosterone deficiency: salt craving, hypovolemia, orthostatic hypotension, hyperkalemia, hyperchloremic acidosis, and azotemia

Androgen deficiency: not important in men; associated with decreased libido and thinning of axillary and pubic hair in women

ACTH-related symptoms: ACTH excess in Addison disease is associated with hyperpigmentation and easy tanning; ACTH deficiency in secondary adrenocortical failure is associated with pallor and the inability to tan

Abbreviation: ACTH, corticotropin.

3 and 10 mcg/dL deserves further testing; greater than 10 mcg/dL makes glucocorticoid insufficiency very unlikely; and greater than 18 mcg/dL excludes the diagnosis.

A very low cortisol level in a patient with symptoms of glucocorticoid insufficiency and signs of cortisol excess (see below) suggests secondary adrenocortical deficiency after withdrawal of supraphysiologic doses of glucocorticoids. In the absence of these symptoms, a low cortisol level in the presence of synthetic glucocorticoids in the blood does not imply glucocorticoid insufficiency.

If the baseline cortisol is between 3 and 10 mcg/dL or exceeds 10 mcg/dL (with strongly suggestive symptoms), the diagnosis of cortisol deficiency is confirmed by a cosyntropin test. After injecting the ACTH (cosyntropin, 250 mcg) intravenously, a plasma cortisol more than 18 mcg/dL essentially rules out longstanding glucocorticoid insufficiency. If the plasma cortisol is less than 18 mcg/dL, a high baseline plasma ACTH concentration indicates primary adrenal disease (Addison disease) and a low or inappropriately normal level indicates secondary failure from hypothalamopituitary insufficiency.

Abnormally high or low concentrations of cortisol-binding globulin (CBG) can give falsely normal or low cortisol values. CBG can be measured if free plasma cortisol assays are not available to sort this out. In addition, cosyntropin test may be falsely negative for a person with recent onset pituitary insufficiency.

Etiologic Diagnosis

Autoimmune adrenalitis is diagnosed with the presence of antibodies against the enzyme 21-hydroxylase. Computed tomographic (CT) imaging of the adrenal glands is helpful in the diagnosis of infectious disorders, adrenal hemorrhage, or malignancy. In the absence of history of exposure to synthetic glucocorticoids, patients with secondary adrenal failure are assessed for other pituitary functions and magnetic resonance imaging (MRI) or CT imaging is performed.

Therapy

Primary adrenocortical failure requires replacement of glucocorticoid and mineralocorticoid hormones, whereas secondary failure requires only glucocorticoid replacement. Patient education is critical and must cover several topics: need for disciplined daily lifelong therapy, increase in the glucocorticoid doses during an acute illness, use of injectable glucocorticoids when oral replacement therapy is not possible, and use of a medical alert identification bracelet or necklace.

Primary Adrenocortical Failure

Glucocorticoid therapy consists of hydrocortisone (10-20 mg in the morning and 5-10 mg in the afternoon) or prednisone (4-5 mg in the morning and 0-2.5 mg in the afternoon). Monitoring ACTH or cortisol concentrations is not reliable for monitoring therapy. Therapy adequacy is assessed through the patient's sense of well-being and the absence of effects of excess glucocorticoids.

Mineralocorticoid therapy consists of fludrocortisone (0.05-0.2 mg orally) and liberal salt intake. The adequacy of replacement is indicated by normal supine blood pressure without a postural decrease on standing up and by the absence of hypertension, edema, and an abnormal potassium concentration. Plasma renin activity in the upper-normal range suggests adequate mineralocorticoid therapy. Mineralocorticoid therapy reduces the glucocorticoid dose and thereby the risks of adverse effects from glucocorticoids.

Acute Illness

In mild to moderate acute illness, the glucocorticoid dose is doubled or tripled and is given at that increased dose for the duration of the illness. If the patient cannot retain oral glucocorticoids because of vomiting, an intramuscular injection of glucocorticoids (eg, dexamethasone 4 mg, hydrocortisone 100 mg, methylprednisolone 20 mg) is administered. In the presence of severe illness, the patient should seek medical attention promptly and be treated with a parenteral glucocorticoid.

For minor procedures performed with local anesthesia and for most radiologic procedures, no special preparation is required beyond a doubling of the patient's oral glucocorticoid dose for that day. For moderately physically stressful procedures, hydrocortisone 50 mg intravenously should be given before the procedure. For major surgery, hydrocortisone 100 mg is given before the induction of anesthesia and is repeated every 6 to 8 hours for the first 24 hours, after which the dose is tapered at a rate that depends on the patient's recovery (usually a decrease in dose by 50% daily to maintenance levels). Because this stress dose of hydrocortisone has adequate mineralocorticoid effect, the use of a specific mineralocorticoid during the acute illness is not necessary.

Adrenal Crisis

For a person not known to have glucocorticoid insufficiency and in whom adrenal crisis is suspected, intravenous access should be established immediately and blood samples collected for measuring electrolyte, glucose, plasma cortisol, and serum ACTH levels. An adrenal crisis requires prompt presumptive management before test results are available. Intravenous saline with dextrose and hydrocortisone (100 mg every 6 hours) should be started. Mineralocorticoid therapy is not necessary at this dose of hydrocortisone. The clinician should search for and treat possible infections and other precipitating causes. After the acute illness is over, the glucocorticoid therapy can be switched to dexamethasone (it will not interfere with plasma cortisol measurements) and the cosyntropin stimulation test performed to evaluate for adrenocortical insufficiency. The glucocorticoid dose is quickly reduced to maintenance dose as the acute condition abates; mineralocorticoid replacement is begun after the saline infusion is stopped.

If the patient is known to have glucocorticoid insufficiency, the glucocorticoid dose is increased promptly to the stress dose until the acute illness is present (usually 3-5 days), and then the dose is rapidly decreased to the maintenance dose. Mineralocorticoid replacement is initiated as soon as the daily dose of hydrocortisone is less than 100 mg.

KEY FACTS

- ✓ Adrenal crisis—dehydration, hypotension, or shock out of proportion to the severity of the current illness
- ✓ Therapy for primary adrenocortical failure—both glucocorticoid and mineralocorticoid replacement
- ✓ Therapy for secondary adrenocortical failure—only glucocorticoid replacement
- ✓ After an adrenal crisis has passed in a patient without glucocorticoid insufficiency, the glucocorticoid therapy should be changed from hydrocortisone to dexamethasone and the cosyntropin stimulation test performed

Cushing Syndrome

Etiologic Factors

Cushing syndrome may have an exogenous or endogenous origin. *Exogenous Cushing syndrome* (more common) is caused by long-term use of supraphysiologic doses of cortisol or other synthetic glucocorticoids.

ACTH-independent endogenous Cushing syndrome is caused by cortisol overproduction by the adrenal cortex. Cortisol overproduction may result from adrenal adenoma (usually <4 cm in diameter); adrenocortical carcinoma (usually >6 cm in diameter) that produces glucocorticoids but also other steroids (eg, adrenal androgens); or rarely, macronodular or micronodular adrenal hyperplasia.

ACTH-dependent endogenous Cushing syndrome is caused by excess ACTH from the pituitary or from an ectopic neuroendocrine tumor. Pituitary ACTH overproduction is caused by a pituitary corticotroph cell adenoma (also called *Cushing disease*). The pituitary adenoma is often not detected on MRI.

The most common causes of endogenous Cushing syndrome are Cushing disease (75%), ectopic ACTH tumors (15%), and adrenal tumors (10%). Ectopic ACTH production from certain tumors (eg, carcinoid tumors) may be clinically indistinguishable from Cushing syndrome caused by pituitary ACTH overproduction. Ectopic ACTH production from malignancy (eg, small-cell lung cancer) is often associated with a rapid increase in cortisol to very high levels, leading to severe metabolic abnormalities (hypokalemia, metabolic alkalosis, hypertension, and hyperglycemia) but not many classical physical features of Cushing syndrome (see below).

Clinical Features

Long-term cortisol excess is associated with the typical clinical features: weight gain and central obesity; thin skin with easy bruisability and wide violaceous striae; plethora; muscle weakness; osteoporosis; cessation of linear growth in growing children or adolescents; lanugo hair; hypertension; hyperglycemia; hypercalciuria and renal stones; and propensity to fungal infections.

Characteristics of modest adrenal androgen excess (eg, acne, hirsutism, menstrual irregularities) are seen with Cushing disease and ACTH-producing bronchial carcinoids. More severe features (virilization) are seen with adrenocortical carcinoma. Characteristics of androgen excess may be absent in patients with Cushing syndrome caused by exogenous glucocorticoid use or with glucocorticoid-producing adrenal adenoma.

ACTH produced in marked quantities may lead to hyperpigmentation.

Extrasellar effects with the rare pituitary corticotroph macroadenomas, bronchopulmonary effects of lung cancer, and abdominal pain caused by adrenocortical carcinoma may point toward the diagnosis.

Diagnosis

If the patient is taking glucocorticoids, no further tests for Cushing syndrome are indicated. A low plasma cortisol level in the presence of clinical features of Cushing syndrome is diagnostic for exogenous exposure to glucocorticoids. Screening for synthetic glucocorticoids may be helpful.

The diagnostic approach to suspected endogenous Cushing syndrome has 2 central components: confirmation of pathologically increased cortisol production and concentration and identification of the cause. Several issues make establishing the diagnosis complex.

Identification of Increased Cortisol Concentration (Hypercortisolemia)

The best screening tests for Cushing syndrome are the overnight 1-mg dexamethasone suppression test (1 mg dexamethasone taken orally at 11:00 PM followed by plasma cortisol at 8:00 AM the next morning), a 24-hour urine collection for free cortisol, and late-night salivary cortisol testing.

After dexamethasone administration, a cortisol value less than 1.8 mcg/dL rules out endogenous hypercortisolemia and a value greater than 5 mcg/dL strongly suggests it, although most patients with endogenous Cushing syndrome have a cortisol of 10 mcg/dL or more. Urinary free cortisol concentration is increased in more than 97% of patients with Cushing syndrome. An increased late-night (11:00 PM) salivary cortisol level suggests the loss of diurnal variation, seen in people with hypercortisolemia. Often, 2 or 3 of these screening tests are performed when Cushing syndrome is suspected. Concordant results greatly increase confidence in the diagnosis.

Pitfalls in Diagnosis of Hypercortisolemia

Many disorders can increase cortisol production and impair the homeostatic mechanisms. These include acute illness of any type, physical stress, obesity, untreated obstructive sleep apnea (OSA), alcoholism, and depression. High urinary free cortisol concentration is also present in people with high urine output. Oral contraceptives can increase CBG (and therefore falsely increase plasma cortisol). Barbiturates, rifampin, and phenytoin use can increase dexamethasone metabolism and therefore cause a falsely positive dexamethasone suppression test result.

No single test is completely reliable to confirm or exclude the diagnosis of Cushing syndrome. Clinicians often rely on repeated measurements of several tests, which are sometimes repeated over an extended period. Cyclic Cushing syndrome causes periods of disease activity (weeks to months) interspersed with periods of inactivity.

Etiologic Diagnosis

Plasma ACTH is suppressed (<5 pg/mL) in patients with adrenal tumors; is within the reference range or modestly increased (<200 pg/mL) in patients with Cushing disease or ectopic ACTH from carcinoids; and is very high (>200 pg/mL) in most patients with ectopic ACTH production from malignancy. A very high plasma ACTH level is often associated with very high plasma and urinary cortisol (more than twice the upper limit of normal) levels. Pituitary MRI is performed if ACTH is not suppressed. If MRI findings are not definitive, inferior petrosal sinus sampling is performed to determine whether the ACTH source is the pituitary region or elsewhere.

Therapy

Treatment of adrenal adenoma and carcinoma is unilateral adrenalectomy. In the presence of life-threatening metabolic complications from hypercortisolemia due to excessive ACTH values, bilateral adrenalectomy may be lifesaving. For Cushing disease, the treatment of choice is transsphenoidal surgical adenomectomy or subtotal hypophysectomy.

If the disease persists, the therapeutic options include pituitary radiotherapy, bilateral adrenalectomy, and use of blockers of steroidogenesis (eg, ketoconazole, mitotane) or the action of glucocorticoids (mifepristone).

In all cases of Cushing syndrome, surgical excision of the causative tumor is followed by cortisol deficiency caused by the suppressed hypothalamic-pituitary adrenal axis. Axis recovery may take up to 1 or 2 years; during this period, the patient needs glucocorticoid replacement therapy.

Primary Aldosteronism

Etiologic Factors

Primary aldosteronism is an autonomous renin-angiotensin–independent disorder caused by idiopathic bilateral hyperplasia (65%), an aldosterone-producing adenoma (30%), unilateral adrenal hyperplasia (<5%), adrenocortical carcinoma (<1%), and, very rarely, the familial disorder glucocorticoid-remediable aldosteronism (<0.1%).

Key Definition

Primary aldosteronism: *excessive secretion of aldosterone that results from an autonomous renin-angiotensin–independent disorder of the zona glomerulosa.*

Clinical Features

The prevalence of primary aldosteronism in the hypertensive population is about 10% (range, 5%-13%). Most patients present with mild to severe hypertension (malignant hypertension is extremely rare). More than 70% of patients with primary aldosteronism may not have the typical unprovoked hypokalemia. Most patients are asymptomatic. Fatigue, muscle weakness, paresthesia, and nephrogenic diabetes insipidus may rarely be present.

Diagnosis

Endocrine Diagnosis

The best screening test is based on measurements of the plasma aldosterone concentration (PAC) (in nanograms per deciliter) and renin activity (PRA) (in nanograms per milliliter per hour). Hypokalemia should be corrected (hypokalemia reduces the aldosterone level), and the patient should not be taking spironolactone and eplerenone (but can be taking the other antihypertensive drugs) at the time of the test. A PAC to PRA ratio greater than 20 in the presence of an elevated plasma aldosterone concentration (>15 ng/dL) is a positive test for primary aldosteronism. Increased PAC and PRA levels with a PAC to PRA ratio less than 10 indicate secondary aldosteronism. Low PAC and PRA levels suggest that another corticosteroid produced in excess (eg, 11-deoxycorticosterone, cortisol) is acting at the mineralocorticoid receptor and is the cause of hypertension and hypokalemia.

The diagnosis of primary aldosteronism is confirmed by showing the nonsuppressible autonomous secretion of aldosterone despite salt loading (ie, oral salt loading, saline infusion, or fludrocortisone suppression test), often with measurement of urinary sodium and urinary aldosterone.

Etiologic Diagnosis

The major challenge of diagnosis is to differentiate unilateral adrenal disorder (an aldosterone-producing adenoma or unilateral adrenal hyperplasia) from bilateral adrenal hyperplasia. Unilateral disease may be treated surgically; however, bilateral hyperplasia is treated medically (see below). This differentiation relies on CT imaging of the adrenals and selective venous sampling.

A unilateral 1- to 2-cm adrenal mass observed on CT scan usually indicates an aldosterone-producing adenoma and is diagnostic in a young person (age <35 years). In older patients or when the mass is not clearly visible or not unilateral, selective adrenal venous sampling is the most helpful in localizing the aldosterone source. After confirmation of reliable adrenal venous catheterization, a unilateral gradient suggests unilateral disease, and the absence of a gradient suggests bilateral hyperplasia. This technically difficult procedure should be performed in medical centers with radiologic expertise.

Differential Diagnosis

Secondary aldosteronism associated with hypertension results from increased renin production as a consequence of renal artery stenosis, malignant hypertension, or a renin-producing tumor. Plasma renin activity, the angiotensin II level, and aldosterone production are increased, and patients present with renin-dependent hyperaldosteronism with hypertension and hypokalemia. Other causes of mineralocorticoid-induced hypertension include excessive black licorice consumption and excess production of 11-deoxycorticosterone or cortisol.

Therapy

Therapy has 3 objectives: control or reverse hypertension, correct hypokalemia, and prevent the toxic effects of excess aldosterone on the cardiovascular system.

Unilateral adrenalectomy is the treatment of choice for aldosteronoma or unilateral hyperplasia unless the patient is at high surgical risk. Surgery corrects hypokalemia in all patients and normalizes blood pressure or significantly improves hypertension in most (98%). Patients with persistent postoperative hypertension should be treated with standard antihypertensive drug therapy.

Medical treatment is indicated for bilateral adrenal hyperplasia and for aldosteronoma if the patient is at high surgical risk. (Surgical treatment of bilateral hyperplasia would require bilateral adrenalectomy to normalize the serum potassium level, but it rarely restores blood pressure to normal levels.) Spironolactone, a mineralocorticoid receptor antagonist, is given at a dosage of 25 to 100 mg once or twice daily. Dose is adjusted for a target serum potassium level near the upper limit of the reference range without the aid of potassium supplements. Spironolactone restores normokalemia and normalizes blood pressure for most patients. Adverse effects include gastrointestinal tract upset, menstrual irregularity in women, and gynecomastia, impaired libido, and impaired potency in men. Women of childbearing age who take spironolactone should use oral contraceptives because the drug may cause feminization of a male fetus through its androgen-blocking effects. Eplerenone, a highly selective mineralocorticoid receptor antagonist with fewer adverse effects, is a good alternative to spironolactone, although eplerenone is more expensive and shorter acting (twice daily dosing is mandatory).

KEY FACTS

✓ Cushing syndrome screening tests—overnight 1-mg dexamethasone suppression test, free cortisol level in 24-hour urine collection, and late-night salivary cortisol testing

✓ Primary aldosteronism classic finding—hypokalemia (but it is a nonspecific finding and is absent in >70% of patients)

Pheochromocytoma and Paraganglioma

Clinical Features

Pheochromocytomas can be asymptomatic (10%-50%), especially with adrenal incidentalomas or when diagnosed during screening of relatives of a person with a genetic syndrome. More commonly, pheochromocytomas are suspected because of the presence of hypertension (particularly when it is labile, paroxysmal, or refractory to treatment) or paroxysmal symptoms of headaches, forceful palpitations, sweating, and pallor. Flushing is not a feature of excess catecholamines. In most patients, the paroxysmal symptoms are stereotypical and vary only in severity or frequency, often getting more severe and more frequent with the duration of the disease. It is important to recognize that most patients with paroxysmal symptoms (so-called spells) do not have pheochromocytoma.

Diagnosis

Endocrine Diagnosis

The biochemical diagnosis of pheochromocytoma requires measurement of fractionated catecholamines and metanephrines in urine over 24 hours and plasma fractionated metanephrines. Creatinine is measured in urine to ensure adequacy of 24-hour collection. In pheochromocytoma, these values are typically increased to more than twice the upper limit of the reference range. A 24-hour urine collection for metanephrines and catecholamines has 90% sensitivity and 98% specificity. Plasma metanephrine levels have 97% to 99% sensitivity but only 85% to 89% specificity. Nevertheless, they provide the best test for patients who have a high pretest probability of the disease, such as those with genetic syndromes. Whereas plasma fractionated metanephrine values in the reference range exclude the diagnosis of pheochromocytoma with a good degree of certainty, increased values often need further confirmation with more specific urinary catecholamines and metanephrines.

Radiologic Localization

Radiologic evaluation helps localize the source after the diagnosis has been established by biochemical confirmation of catecholamine excess. CT imaging and MRI of the abdomen (and if findings are negative, CT and MRI of the pelvis, thorax, and neck) are the mainstays of radiologic localization. They have a sensitivity and specificity greater than 90%. On MRI, pheochromocytomas show high signal intensity on T2-weighted images. CT provides better spatial resolution. CT with nonionic contrast medium is considered the first radiologic procedure of choice.

Therapy

Surgical excision of the pheochromocytoma is curative. Blood pressure is controlled to diminish perioperative morbidity and death. α-Adrenergic blockade with phenoxybenzamine is instituted as soon as the diagnosis is made and is followed with calcium channel blockers (nifedipine or amlodipine) if needed to improve the control of blood pressure. The target for blood pressure while seated is the low-normal range for the patient's age. β-Adrenergic blockers (propranolol or metoprolol) may be necessary to control tachycardia (target, 80 beats per minute), but β-blockade should be used only after adequate α-blockade has been established. β-Adrenergic blockade without α-adrenergic blockade could exacerbate or even precipitate malignant hypertension. For hypertensive emergencies, intravenous phentolamine (an α-blocker) is the drug of choice and can be given in 5- to 10-mg doses every 5 to 15 minutes as needed. Alternatively, nitroprusside can be used.

Adrenal Incidentaloma

Etiologic Factors

Small (1- to 6-cm) adrenal masses are found in up to 9% of unselected autopsies and in more than 2% of all abdominal imaging studies. Most are nonfunctioning adenomas; a few are functioning adenomas or carcinomas of the adrenal cortex or medulla. Metastasis to the adrenal glands is commoner than expected from the size of the glands. Identification of the nature of the mass is important: Nonfunctioning adenomas are harmless, a functioning adenoma or a carcinoma requires surgery, and metastasis requires oncologic care.

Diagnosis

The diagnosis of a functioning adrenal tumor rests on clinical evaluation, screening tests, and when appropriate, confirmatory tests. For all patients, hormonal evaluation should screen for pheochromocytoma (24-hour urinary fractionated catecholamines and metanephrines) and Cushing syndrome (overnight 1-mg dexamethasone suppression test). Dehydroepiandrosterone-sulfate (DHEA-S) should also be measured. Plasma renin activity and plasma aldosterone concentration should be measured in hypertensive patients. If the results of these screening tests imply a particular hormonal abnormality, appropriate confirmatory tests are required.

Often, CT scans without and with radiocontrast medium are performed with an adrenal protocol to further characterize the incidentally diagnosed adrenal mass. Radiodensity less than 10 Hounsfield units on CT scan, a homogeneous appearance, lack of vascularity, and a well-defined border are strong indicators that the tumor is benign. Other than showing the fat density of an adrenal myelolipoma, imaging studies may not differentiate between benign and malignant neoplasms. A mass 4 cm or larger has a greater chance of being malignant. On dynamic contrast data of the CT scan, a contrast wash-out of 50% or more within 10 minutes implies that the tumor is benign. On MRI, bright T2 images suggest pheochromocytoma or adrenal cancer.

If an incidental adrenal mass is identified in a patient who has an active malignancy and with a chance that the mass is metastatic, further investigation is indicated only if the diagnosis of the mass will change the management strategy for the malignancy. Needle aspiration of the mass may then be performed but only after excluding pheochromocytoma. Otherwise, needle biopsy of an adrenal adenoma is never indicated.

Therapy

All functional adrenal masses, all masses 6 cm or larger, and all masses with radiologic features consistent with malignancy should be excised after appropriate preparations. Surgical excision is not needed for nonfunctional adrenal masses smaller than 4 cm with clearly benign imaging phenotype.

KEY FACTS

- ✓ Pheochromocytoma biochemical diagnosis—24-hour urinary fractionated catecholamines and metanephrines and plasma fractionated metanephrines
- ✓ Pheochromocytoma therapy—if control of tachycardia requires β-blockers, first the adequacy of α-blockade should be ensured (to avoid exacerbation or precipitation of malignant hypertension)
- ✓ Small adrenal masses (1-6 cm in diameter) found incidentally in autopsies (≤9%) or abdominal imaging studies (>2%)—usually nonfunctioning adenomas
- ✓ Hormonal evaluation for diagnosis of functioning adrenal tumor—screen for pheochromocytoma and Cushing syndrome and measure DHEA-S; for a hypertensive patient, also measure plasma renin activity and plasma aldosterone concentration
- ✓ After pheochromocytoma has been excluded, needle biopsy of an incidental adrenal mass is indicated only if the mass may be metastatic in a patient who has active malignancy and the mass diagnosis would change the management of the malignancy

Disorders of the Testis

Male Hypogonadism in the Adult

Male hypogonadism refers to the clinical presentations resulting from diminished testosterone action (Box 14.2).

Etiologic Factors

The etiologic factors of male hypogonadism are outlined in Table 14.1.

Diagnosis

If the present clinical characteristics are strong for hypogonadism, the diagnosis is established by documenting very low morning serum total testosterone concentrations. If the suspicion is moderate, a low morning serum total testosterone concentration should be reconfirmed before making a diagnosis. Evening testosterone is normally low in healthy men. Total testosterone concentration may not be reliable with abnormal concentration of sex hormone–binding globulin (eg, decreased concentration with aging and obesity, increased concentration with aging and excess estrogen), and therefore free (or bioavailable) testosterone may be measured. Benefits of treating low testosterone seen with aging are not clear.

OSA should be adequately treated before confirmation of the diagnosis and consideration of the treatment of hypogonadism.

Box 14.2 • Clinical Manifestations of Male Hypogonadism

- More specific symptoms and signs
  - Incomplete or delayed sexual development, eunuchoidism (long limbs)
  - Reduced sexual desire (libido) and activity
  - Decreased spontaneous erections
  - Breast tenderness, gynecomastia
  - Loss of body hair (axillary and pubic), reduced shaving frequency
  - Very small (especially <5 mL) or shrinking testes
  - Infertility, sperm count low or zero, decreased ejaculate volume
  - Height loss, low-trauma fracture, low bone mineral density (osteoporosis)
  - Hot flushes, sweats (especially if rapid onset)
- Less specific symptoms and signs
  - Decreased energy, motivation, initiative, and self-confidence
  - Feeling sad or blue, depressed mood, dysthymia
  - Poor concentration and memory
  - Sleep disturbance, increased sleepiness
  - Mild anemia (normochromic, normocytic; in the female range)
  - Reduced muscle bulk and strength
  - Increased body fat, feminine fat distribution, increased BMI
  - Diminished physical or work performance
  - Classic hypogonadal facies (with pallor and fine wrinkling around the mouth and eyes)

Abbreviation: BMI, body mass index.

Modified from Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al; Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010 Jun;95(6):2536-59; used with permission.

Therapy

Contraindications for testosterone therapy include prostate cancer, breast cancer, elevated hematocrit level (>50%), uncontrolled OSA, severe lower urinary tract symptoms, prostate-specific antigen level of more than 4 ng/mL (or >3 ng/mL with a family history of prostate cancer), or poorly controlled heart failure.

In men, androgen therapy is aimed at restoring and maintaining androgenic functions by replacing and normalizing the serum total testosterone concentration. In hypogonadal pubertal boys, androgen therapy is designed to initiate and induce full pubertal development; therapy is started at a smaller dose than for men and titrated upward over time to prevent behavioral changes associated with full replacement. Venous thromboembolism, fluid retention, elevations in hematocrit levels, OSA, and worsening prostatic symptoms have been described with testosterone therapy. Monitoring such concerns during testosterone replacement therapy (Table 14.2) is beneficial. Additionally, azoospermia is expected with exogenous testosterone therapy.

Androgen replacement may be in various forms (Table 14.3). Intramuscular testosterone therapy, often started at 200 mg per dose, leads to a substantially high testosterone level soon after the injection and to a decrease before the next dose. Other modes of delivery provide more stable testosterone concentrations.

Oral preparations of testosterone are not used for replacement in the United States because of the fear of induction of peliosis hepatis and hepatic tumors.

Adverse effects of testosterone replacement therapy include acne, mild weight gain, edema, increased erythropoiesis, and induction or worsening of OSA. Monitoring of therapy is important (Tables 14.2 and 14.3).

Infertility associated with hypergonadotropic hypogonadism rarely can be managed with assisted reproductive technologies, such as intracytoplasmic sperm injection. Mostly, donor sperm and adoption are the only options. Treatment of infertility in a person with hypogonadotropic hypogonadism necessitates the use of luteinizing hormone (LH), follicle-stimulating hormone (FSH), or their agonists.

Gynecomastia

Etiologic Factors

Gynecomastia refers to a benign enlargement of the male breast caused by an increase in glandular and stromal tissues due to an

Table 14.1 • Causes of Testosterone Deficiency

Characteristics	Testosterone Resistance[a]	Testosterone Deficiency[a]: Primary Testicular Dysfunction (Hypergonadotropic Hypogonadism)	Testosterone Deficiency[a]: Hypothalamic-Pituitary Dysfunction (Central or Hypogonadotropic Hypogonadism)
Testosterone level	High normal	Low	Low
LH and FSH levels	High normal	Very high	Normal or low
Causes			
Genetic	Androgen receptor defect	Klinefelter syndrome	Kallmann syndrome
Drugs	Spironolactone, flutamide, finasteride	Ketoconazole	Neuroleptic agents, antidepressants
Trauma/structural	–	Bilateral testicular trauma, radiotherapy, chemotherapy (busulfan, vincristine) Mumps, autoimmune testicular failure	Hypothalamopituitary mass, inflammatory disease, hemorrhage
Functional	–	–	Constitutional delay in puberty; untreated OSA
Degenerative	–	Myotonia dystrophica	–
Nutritional	–	–	Severe malnutrition
Endocrinopathy	–	–	Hyperprolactinemia, severe thyroid dysfunction, adrenocortical dysfunction

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone; OSA, obstructive sleep apnea.

[a] Dash indicates not applicable.

Table 14.2 • Monitoring During Testosterone Replacement Therapy

Feature of Concern	Method of Monitoring
Symptoms review	3 and 6 months and yearly after initiation
Testosterone concentration	3 and 6 months and yearly (Table 14.3)
Polycythemia	Hematocrit: baseline, 3 to 6 months, and yearly. Stop therapy if hematocrit exceeds 54%; restart after hematocrit normalization and treating other causes of hypoxia
Bone mineral density	1 to 2 years after initiation (if osteoporosis)
Prostate	If baseline PSA greater than 0.6 ng/mL: digital rectal examination[a] and PSA test: baseline at 3 to 6 months and yearly test thereafter Baseline PSA is PSA at 6 months after initiation Clinically significant changes after 6 months: PSA increase more than 1.4 ng/mL over 1 year *or* PSA rate of increase more than 0.4 ng/mL yearly (for >2 years)[a] Lower urinary tract symptom assessment for important change: AUA/IPSS >19[a]
OSA	History (Epworth Sleepiness Scale); overnight oximetry as indicated
Dyslipidemia	Fasting triglycerides
Gynecomastia	History, examination; mammography if indicated
Local problems	History, examination of site of testosterone delivery

Abbreviations: AUA, American Urological Association; IPSS, International Prostate Symptom Score; OSA, obstructive sleep apnea; PSA, prostate-specific antigen.

[a] Obtain urology consultation.

Table 14.3 • Monitoring Testosterone Concentration During Testosterone Replacement Therapy

Treatment Modality	Starting Dose and Frequency of Use	Schedule for Measuring Testosterone Level
Injectable testosterone (enanthate or cypionate)	Starting 300 mg every 2 to 4 weeks	Midway between injections
Transdermal patches	2.5 to 7.5 mg daily	Within 3 to 12 hours after application of the patch
Buccal testosterone	30 mg every 12 hours	Immediately before or after application of a fresh system
Transdermal gels	2.5 to 7.5 mg daily	Any time after 1 or more weeks of treatment
Testosterone pellets	4 pellets of 75 mg each every 3 to 6 months	At end of dosing interval

increase in the estrogen to androgen ratio. The increased ratio results from androgen deficiency, exposure to exogenous estrogen, exposure to exogenous testosterone (which is converted to estrogen in the body), or an endogenous increase in estrogen production. In pubertal boys, gynecomastia is physiologic. In men, the most common causes are drugs and alcohol-related liver disease. In about 10% of cases, the cause of gynecomastia is indeterminate or idiopathic. Identifying a cause may unravel a serious systemic illness (Box 14.3).

Key Definition

Gynecomastia: *benign enlargement of the male breast caused by an increase in glandular and stromal tissues.*

Box 14.3 • Causes of Gynecomastia

- Primary hypogonadism (testicular failure)
- Puberty
- Aging
- Refeeding in severe, long-standing malnutrition
- Renal failure and dialysis
- Hepatic cirrhosis
- Hyperthyroidism
- Hormonal abnormalities (excess estrogens, exogenous testosterone, elevated levels of hCG or prolactin)
- Drugs (eg, ketoconazole, spironolactone, metronidazole)
- Other substances (eg, alcohol, marijuana)

Abbreviation: hCG, human chorionic gonadotropin.

Diagnosis

If gynecomastia is bilateral, the clinician can exclude pseudogynecomastia (fatty enlargement). If it is unilateral, the clinician can exclude cancer of the breast (signs of breast cancer are eccentric location in relation to the areola, firm distinct mass, fixation, ulceration, bloody nipple discharge, and presence of axillary lymphadenopathy). Mammography and excisional biopsy may be needed.

A complete medical history, physical examination, and appropriate laboratory studies should be performed to determine the cause of gynecomastia and therefore the path of management. Endocrine tests may include measurement of the serum levels of testosterone, estradiol, LH and FSH, β-human chorionic gonadotropin, sensitive thyrotropin, DHEA-S, and prolactin.

Therapy

Gynecomastia of puberty is often only minimal. Indications for surgery include cosmetic correction and malignancy (or suspicion of malignancy).

KEY FACTS

- ✓ Testosterone levels in many older men are less than in young men, but the apparent decrease in total serum testosterone in men >50 years is less than the decrease in free testosterone levels because sex hormone–binding globulin increases with age
- ✓ Contraindications for testosterone therapy—prostate cancer or breast cancer
- ✓ Oral testosterone (not used in the United States)—less effective and more expensive than other forms (intramuscular injection, transdermal patch, or gel) and associated with hepatotoxicity, peliosis hepatis, and hepatic tumors
- ✓ Gynecomastia—most common breast disorder in pubertal boys and men (>85% of breast masses are in boys and men)

Disorders of the Ovary

Amenorrhea

Primary amenorrhea is present when menarche has not occurred by age 15 years (or within 5 years of the first sign of puberty). *Secondary amenorrhea* is present when previously established menstrual function stops for more than 3 months.

Etiologic Factors

Normal regular menstrual function has several requirements (Box 14.4). Amenorrhea can be physiologic or pathologic (Box 14.5).

Box 14.4 • Requirements for Normal Regular Menstrual Function

- Normal cyclic secretion of hypothalamic gonadotropin-releasing hormone and the pituitary gonadotropins, luteinizing hormone and follicle-stimulating hormone
- Normal ovarian follicular apparatus that responds to cyclic gonadotropin stimulation by ovulation and production of estrogen and progesterone in a cyclic manner
- Normal endometrium capable of responding to estradiol (follicular proliferative endometrium) and progesterone (luteal secretory endometrium) and then to their decreasing concentrations by the initiation of menstrual shedding

Clinical Characteristics

In addition to amenorrhea, estrogen deficiency may cause decreased vaginal secretions and dyspareunia, hot flushes, osteopenia, and lack of development or a regression of secondary sex characteristics. Other clinical features are related to the cause, such as hyperandrogenic features (eg, polycystic ovary syndrome [PCOS]), expressible or spontaneous galactorrhea (high prolactin concentrations), and short stature or other features related to Turner syndrome, hypothyroidism, goiter, and other manifestations of hypopituitarism.

Diagnosis

The diagnostic approach to secondary amenorrhea is summarized in Box 14.6.

Therapy

Management of amenorrhea is directed at the underlying disorder and restoration of a eugonadal state. The cause should be identified and treated. If the cause cannot be treated successfully, hypogonadism (resulting in low estrogen level) should be corrected with estrogen replacement (with or without progesterone). If feasible, ovulation and fertility potential should be restored.

Estrogen Replacement

The goals of estrogen therapy include control of vasomotor instability, prevention of genitourinary atrophy, preservation of secondary sex characteristics, prevention of osteoporosis, and restoration of a sense of well-being.

Absolute contraindications to estrogen therapy include known or suspected estrogen-dependent neoplasm (breast or endometrial), cholestatic hepatic dysfunction, active thromboembolic disorder, history of thromboembolic disorder associated with previous use of estrogen, neuro-ophthalmologic vascular disease, and undiagnosed vaginal bleeding.

Box 14.5 • Causes of Amenorrhea

Physiologic causes

- Pregnancy
- Lactation
- Menopause

Pathologic causes

- Functional hypothalamic-pituitary disorders
  - Nutritional disorder^{P,S}
  - Severe emotional stress^{P,S}
  - Prolonged heavy exercise^{P,S}
  - Competitive athletics^{P,S}
  - Systemic illness^{P,S}
  - Severe weight loss^{P,S}
  - Other endocrinopathies
    - Uncontrolled diabetes mellitus^{P,S}
    - Hyperprolactinemia^{P,S}
    - Severe thyroid disorders^{P,S}
    - Severe adrenal disorders^{P,S}
    - Hyperandrogenic state caused by an adrenal or ovarian disorder^{P,S}
- Organic hypothalamic-pituitary disorders
  - Destruction of pituitary gonadotrophs^{P,S}
  - Postpartum pituitary necrosis (Sheehan syndrome)^{S}
  - Hyperprolactinemia^{P,S}
- Ovarian disorders
  - Turner syndrome$^{P,\text{ rarely } S}$
  - Acquired ovarian disorders^{P,S}
  - Polycystic ovary syndrome^{S}
  - Premature ovarian failure (primary premature ovarian insufficiency)^{S}
  - Autoimmune oophoritis^{S}
  - Abdominal radiotherapy^{P,S}
  - Chemotherapy^{P,S}
  - Hormone-producing tumors (estrogen, androgen, or human chorionic gonadotropin)^{P,S}
- Uterus and outflow tract disorders
  - Müllerian duct agenesis^{P}
  - Imperforate hymen^{P}
  - Isolated absence of the uterus^{P}
  - After endometrial ablation^{S}
  - Vaginal aplasia or atresia^{P}
  - Pelvic inflammatory disorders^{P,S}

Abbreviations: P, primary; S, secondary amenorrhea.

Box 14.6 • Diagnostic Approach to Secondary Amenorrhea

1. Rule out physiologic amenorrhea (pregnancy test), genital tract outflow disorders (clinical evaluation, hysteroscopy)
2. Rule out PRL and hyperandrogenic state (clinical evaluation, serum levels of testosterone and DHEA-S)
3. Measure serum levels of estradiol, LH, and FSH to distinguish ovarian disease from hypothalamic-pituitary disease
4. Low serum levels of estradiol and increased levels of FSH and LH suggest primary ovarian failure. Obtain a karyotype if the patient is younger than 30 years
5. Low serum levels of estradiol and inappropriately low levels of FSH and LH suggest a hypothalamic-pituitary disorder. Rule out a functional disorder and organic hypothalamic pituitary disease
6. If organic disease is not identified, consider amenorrhea to be of indeterminate cause and pursue long-term follow-up

Abbreviations: DHEA-S, dehydroepiandrosterone-sulfate; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PRL, hyperprolactinemia.

Estrogen therapy must be individualized and administered only after a thorough discussion with the patient about its benefits and risks. Therapy is initiated as soon as possible after the diagnosis of estrogen deficiency and is continued indefinitely or until the cause has been reversed.

Estrogen preparations include oral estradiol (0.5-2.0 mg daily), oral conjugated estrogens (0.625-1.25 mg daily), and transdermal estradiol patch (0.025-0.10 mg estradiol daily). Oral progestational agents are used for a woman with an intact uterus (medroxyprogesterone acetate 10 mg daily or progesterone 200 mg daily) for days 1 to 12 of each month. Oral and transdermal hormonal combinations are also available.

Complications of estrogen replacement include increased risk (4- to 8-fold) of endometrial cancer (usually stage I, with no excess mortality risk), depending on dose and duration. This risk is prevented by progestin supplementation. Other possible adverse effects include a slightly increased risk of breast cancer (breast examination and mammography before treatment and annually thereafter are essential) and increased risk of surgical gallbladder disease.

Ovulation Induction

Women without ovarian failure and with infertility from anovulation can be given clomiphene citrate, exogenous gonadotropin, or gonadotropin-releasing hormone therapy. The drug of choice for infertility with hyperprolactinemia is the dopamine-agonist bromocriptine.

Box 14.7 • Polycystic Ovary Syndrome (PCOS)

PCOS is characterized by the presence of 2 of the following 3 criteria:

Ovulatory dysfunction (anovulation: infrequent bleeding with cycles >35 days, <8 cycles yearly, or rarely, frequent bleeding with cycles <21 days); for adolescents, anovulatory cycles are normal and are not used as a criterion

Clinical or biochemical evidence of hyperandrogenism (hirsutism, male pattern baldness, or elevated serum testosterone level)

Polycystic changes in the ovaries (≥1 ovary with 12 follicles of 2-9 mm or volume >10 mL in the absence of a dominant follicle >10 mm)

Polycystic Ovary Syndrome

PCOS is the most common cause of nonvirilizing hyperandrogenicity. It is characterized by the presence of specific criteria, listed in Box 14.7.

Etiologic Factors

The pathogenesis is poorly understood. Gonadotropin dynamics are abnormal, with loss of the LH surge and increased LH levels. Hyperandrogenicity is mild to moderate and LH dependent.

Clinical Characteristics

Many patients have an associated obesity and insulin resistance with consequent hyperinsulinism, which further contribute to the androgen excess. Insulin resistance may be present without obesity. The degree of insulin resistance varies. Many women have a mild form; severe insulin resistance is usually appreciated clinically by the presence of acanthosis nigricans.

The onset of PCOS is at puberty, and its progression is slow and mild. Hirsutism (70% of patients), menstrual abnormality (88%), infertility and anovulation (75%), and obesity (50%) are usually present. The serum level of testosterone is within the reference range or modestly increased (70% of patients) and is nearly always less than 200 ng/dL. DHEA-S levels are within the reference range or mildly increased in 25% of patients. Changes on pelvic ultrasonography are characteristic (70%), and hyperprolactinemia may be present in 25% to 30% of patients. Of note, anovulation exposes the endometrium to unopposed estrogen, which increases the risk of endometrial hyperplasia and cancer.

Diagnosis

The diagnosis of PCOS is one of exclusion of other causes of hyperandrogenism. These causes include hypothyroidism, hyperprolactinemia, late-onset congenital adrenal hyperplasia, pregnancy, Cushing syndrome, androgen-secreting tumors of the ovaries or adrenals, and primary ovarian failure.

Box 14.8 • Causes of Hyperprolactinemia

- Physiologic
  - Lactation
  - Pregnancy
  - Sleep
  - Stress
  - Coitus
  - Exercise
- Pharmacologic
  - Anesthetics
  - Anticonvulsants
  - Antidepressants and other psychotropic medicines
  - Antihistamines (H_2 receptor antagonists)
  - Antihypertensives
  - Cholinergic agonists
  - Estrogens: oral contraceptives, oral contraceptive withdrawal
  - Opiates and opiate antagonists
- Pathologic
  - Hypothalamic–pituitary stalk damage: hypothalamic or suprasellar damage, pituitary mass or injury
  - Pituitary disorders: acromegaly, plurihormonal adenoma, prolactinoma
  - Systemic disorders: primary hypothyroidism, chest nerve irritation, chest wall trauma, herpes zoster infection, chronic renal failure, cirrhosis, epileptic seizures

Modified from Melmed S, Kleinberg D. Anterior pituitary. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR, editors. Williams textbook of endocrinology. 11th Ed. Philadelphia (PA): Saunders Elsevier; c2008. p. 155-261; used with permission.

Therapy

Treatment of PCOS involves increased exercise, weight loss, metformin use, and if needed, specific treatment at infertility clinics.

Disorders of Prolactin: Hyperprolactinemia

Amenorrhea, galactorrhea, infertility, pituitary mass, or hirsutism often leads to measurement of prolactin. Hypogonadism caused by elevated prolactin levels can cause osteoporosis. Prolactin concentrations are normally higher in women than men; therefore, sex-specific reference ranges should be used to interpret the results.

If asymptomatic patients have high prolactin concentrations, macroprolactin should be measured. Macroprolactin is a biologically inactive immunoglobulin G–bound prolactin with no clinical significance.

After the history (including a drug history) and physical examination, the common causes of hyperprolactinemia should be excluded with testing for thyrotropin level (to rule out primary hypothyroidism), pregnancy, and creatinine level (Box 14.8).

If no other cause of hyperprolactinemia is found, MRI of the head is performed to evaluate the pituitary-hypothalamic region.

Secondary causes of hyperprolactinemia should be appropriately treated. The treatment plan for hyperprolactinemia depends on the purpose of therapy (Box 14.9).

Box 14.9 • Treatment of Hyperprolactinemia

Prolactin-producing pituitary adenoma—treat with dopamine agonist (cabergoline or bromocriptine) at a dose that normalizes prolactin concentrations for 1 or more years; treatment is withdrawn if the tumor disappears and prolactin level remains within the reference range after discontinuation of the dopamine agonist

Galactorrhea—if socially embarrassing, treat with dopamine agonist

Amenorrhea caused by hyperprolactinemia—treat with cyclic estrogen-progesterone tablets to avert the harmful effects of hypogonadism

Asymptomatic, physiologic, drug-induced, or stress-induced hyperprolactinemia—no therapy (mild hyperprolactinemia, even with expressive galactorrhea, may normally occur in premenopausal women who have had babies)

Potentially vision-threatening pituitary macroadenoma in patients with intolerance to dopamine agonists—treat with pituitary surgery

KEY FACTS

✓ Absolute contraindications to estrogen therapy—estrogen-dependent neoplasm, cholestatic hepatic dysfunction, active thromboembolic disorder, previous thromboembolic disorder with use of estrogen, neuro-ophthalmologic vascular disease, and undiagnosed vaginal bleeding

✓ Diagnosis of PCOS—exclusion of other causes of hyperandrogenism (eg, hypothyroidism, hyperprolactinemia, late-onset congenital adrenal hyperplasia, pregnancy, Cushing syndrome, androgen-secreting tumors of the ovaries or adrenals, primary ovarian failure)

✓ High prolactin levels in asymptomatic patients—may reflect macroprolactinemia

15

Lipid Disorders

EKTA KAPOOR, MBBS

Etiologic Factors

Lipid disorders result from genetic abnormalities in lipoprotein metabolism, other medical conditions (eg, type 2 diabetes mellitus, nephrotic syndrome, hypothyroidism, excessive alcohol use), and use of certain drugs (eg, corticosteroids, immunosuppressants) (Box 15.1). The characteristics of genetic dyslipidemias are outlined in Tables 15.1 and 15.2. The most common disorders in this group are those of low-density lipoprotein (LDL) cholesterol (LDL-C), which often lead to premature atherosclerosis in persons and their family members.

Clinical Features

Hyperlipidemia is typically asymptomatic and is diagnosed on screening. Patients usually do not have physical findings directly attributable to hyperlipidemia; however, some patients have eyelid xanthelasmata and arcus corneae.

Extreme increases in LDL-C, as noted in familial hypercholesterolemia, may cause **tendon xanthomas** (papules and nodules in the tendons of the hands and feet and the Achilles tendon). **Palmar xanthomas** (yellowish plaques involving the palms and flexural surfaces of the fingers) occur in hyperlipoproteinemia type II and type III. Hyperchylomicronemia can cause **eruptive xanthomas** (small, yellowish orange to reddish brown papules).

Key Definitions

Tendon xanthomas: *papules and nodules in the tendons of the hands and feet and the Achilles tendon.*

Palmar xanthomas: *yellowish plaques on the palms and flexural surfaces of the fingers.*

Eruptive xanthomas: *small yellowish orange to reddish brown papules.*

Increased LDL-C and lipoprotein (a), also known as *Lp(a)*, and decreased high-density lipoprotein cholesterol (HDL-C) confer increased risk of atherosclerotic cardiovascular disease (ASCVD). Increased HDL-C is associated with decreased atherogenic risk. Hypertriglyceridemia may be atherogenic by inducing alterations in other lipoproteins. Triglycerides likely also have an unidentified direct atherogenic action. Pancreatitis may develop with very high triglyceride concentrations (generally >1,000 mg/dL).

Diagnosis and Screening

Disorders of lipoprotein metabolism predispose to premature coronary heart disease (CHD) and vascular disease, and CHD is the leading cause of death in developed nations. Although dyslipidemia is a modifiable risk factor for cardiovascular disease (CVD), it usually is asymptomatic. Experts therefore recommend screening for it in appropriate patients. This strategy aids risk stratification of patients to identify those who would benefit from interventions, including lipid-lowering therapy. LDL-C has conventionally been the target of lipid-lowering therapy, but that alone is a poor predictor of CHD risk. Most current risk-prediction models also use total cholesterol and HDL-C levels in their calculations.

Released in 2013, the updated American College of Cardiology (ACC)/American Heart Association (AHA) guidelines replaced the Adult Treatment Panel (ATP III) guidelines. The ACC/AHA guidelines recommend assessment of risk factors, including smoking, hypertension, diabetes mellitus, total cholesterol, and HDL-C, every 4 to 6 years for patients aged 20 to 79 years who are free of CVD. This assessment is used to calculate the 10-year CVD risk (with the Pooled Cohort Equations Cardiovascular Risk Calculator). The US Preventive Services Task Force recommends dyslipidemia screening every 5 years starting at age 35 years for men and at age 45 years for women.

Box 15.1 • Causes of Secondary Hyperlipidemia

- Increased LDL-C
  - Hypothyroidism
  - Nephrotic syndrome
  - Cholestatic liver disease
  - Progestin use
  - Anabolic steroid use, glucocorticoid therapy
  - Anorexia nervosa
  - Acute intermittent porphyria
- Increased triglycerides
  - Obesity
  - Diabetes mellitus
  - Hypothyroidism
  - Sedentary lifestyle
  - Excessive alcohol use
  - Renal insufficiency
  - Estrogen treatment
  - β-Blocker therapy
  - Use of thiazides or corticosteroids
  - Dysglobulinemia
  - Systemic lupus erythematosus
- Decreased HDL-C
  - Hypertriglyceridemia
  - Obesity
  - Diabetes mellitus
  - Cigarette smoking
  - Sedentary lifestyle
  - β-Blocker therapy
  - Progestin treatment
  - Anabolic steroid use

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Therapy

Lipid-Lowering Therapy for ASCVD Reduction

Statins are the cornerstone of lipid-lowering therapy for ASCVD reduction. This drug group is the only class of lipid-lowering agents that has consistently decreased CVD risk. Statins are used for both primary and secondary prevention of CVD. They mainly decrease levels of LDL-C. Depending on the type of statin and the dose used, statins can decrease triglyceride levels by 20% to 40%. They have been classified into high-, moderate-, and low-intensity therapy on the basis of their predicted LDL-C–lowering ability. Examples of statins, categorized by their intensity, are listed in Table 15.3. Fibrates and niacin have not resulted in any convincing improvement in clinical outcomes, and niacin may actually increase adverse cardiovascular outcomes.

Primary Prevention of ASCVD

The 2018 ACC/AHA guideline for the management of blood cholesterol provides specific treatment algorithms for primary prevention of ASVCD (Figure 15.1). Of patients with a very high LDL-C level (≥190 mg/dL) and those with diabetes, all should receive statin therapy. For patients age 40 to 75 years with an LDL-C value between 70 and 190 mg/dL and no diabetes, the 10-year ASVCD risk percent is calculated. Next steps for risk reduction are determined on the basis of this risk calculation and the presence or absence of risk-enhancing factors (Box 15.2).

Secondary Prevention of ASCVD

The 2018 ACC/AHA guideline for the management of blood cholesterol categorizes patients with a history of ASCVD into groups of not very high risk and very high risk (Box 15.3). The treatment algorithm for secondary prevention of ASVCD recommends statin therapy for all these patients (Figure 15.2). If specific LDL-C goals are not reached by some patients, initiation of additional treatments, including ezetimibe or PSCK9 inhibitors, may be indicated.

Therapeutic Lifestyle Changes

Healthy dietary habits, regular exercise, weight management, and smoking cessation should be recommended to all patients with elevated CVD risk regardless of whether they are candidates for statin therapy. The AHA step 1 diet recommends limiting dietary fat intake to 30% or less of total calories, with less than 10% of calories from saturated fat, and avoidance of trans fatty acids. Alcohol restriction can decrease triglyceride concentrations. The AHA recommends moderate-intensity aerobic activity for at least 150 minutes weekly.

KEY FACTS

- ✓ Causes of lipid disorders—genetic abnormalities, various medical conditions, and certain drugs
- ✓ Dyslipidemia—usually asymptomatic, but a modifiable risk factor for CVD
- ✓ ACC/AHA criteria for consideration of statin therapy in 4 high-risk groups—1) known ASCVD; 2) LDL-C ≥190 mg/dL; 3) diabetes mellitus, age 40-75 years, and LDL-C 70-189 mg/dL; and 4) ≥7.5% 10-year risk of cardiac event or stroke
- ✓ ACC/AHA recommendation—do not treat with statins to reach specific LDL-C or non–HDL-C goals

Table 15.1 • Features of Primary Hyperlipidemias: Familial Hypercholesterolemia, Combined Hyperlipidemia, and Dysbetalipoproteinemia

Features	**Familial Hypercholesterolemia**[a]	**Familial Combined Hyperlipidemia**	**Familial Dysbetalipoproteinemia**
Pathophysiologic factors	Defective LDL receptor or defective apo B_{100}; impaired catabolism of LDL	Complex; in some cases, overproduction of apo B_{100}	Defective or absent apo E; excess of CM remnants and VLDL in fasting state
Mode of inheritance	Autosomal codominant	Autosomal dominant	Autosomal recessive
Estimated population frequency	Heterozygotes: 1:500 Homozygotes: 1:1 million	1:50 to 1:100	1:5,000
Risk of CHD	+++	++	+
Physical findings	Arcus corneae Tendinous xanthomas	Arcus corneae	Arcus corneae Tuberoeruptive and palmar xanthomas
Associated findings	–	Obesity Glucose intolerance Hyperuricemia HDL-C deficiency Increased apo B_{100}	Obesity Glucose intolerance Hyperuricemia
Treatment	Diet Statins Ezetimibe Bile acid–binding resins LDL apheresis	Diet Drugs singly or in combination with niacin, statin, gemfibrozil, resin	Diet Niacin Gemfibrozil Statin

Abbreviations: apo B, apolipoprotein B; CHD, coronary heart disease; CM, chylomicron; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; +++, very high risk; ++, high risk; +, moderate risk.

[a] Dash indicates not applicable.

Table 15.2 • Features of Primary Hyperlipidemias: Hypertriglyceridemia

		Severe Hypertriglyceridemia	
Features	**Familial Hypertriglyceridemia**	**Early Onset**	**Adult Onset**
Pathophysiologic factors	Overproduction of hepatic VLDL-Tg but not of apo B_{100}	Lipoprotein lipase deficiency Apo C-II deficiency; defect in CM and VLDL catabolism	Overproduction of hepatic VLDL-Tg Delayed CM and VLDL catabolism
Mode of inheritance	Autosomal dominant	Autosomal recessive	Autosomal recessive
Estimated population frequency	1:50	<1:10,000	Rare
Risk of CHD	+ In families with HDL-C deficiency	–	+
Physical findings	None	Lipemia retinalis Eruptive xanthomas	Milky plasma Lipemia retinalis Eruptive xanthomas Pancreatitis
Associated findings	Obesity Glucose intolerance Hyperuricemia HDL-C deficiency	HDL-C deficiency Recurrent abdominal pain Pancreatitis Hepatosplenomegaly	Obesity Glucose intolerance Hyperuricemia HDL-C deficiency Pancreatitis
Treatment	Diet Niacin Gemfibrozil Abstinence from alcohol, estrogen	Diet Fish oil	Diet Control diabetes when present Avoidance of alcohol, estrogen Gemfibrozil Fish oil

Abbreviations: apo B, apolipoprotein B; CM, chylomicron; HDL-C, high-density lipoprotein cholesterol; VLDL, very low-density lipoprotein; VLDL-Tg, very low-density lipoprotein triglycerides; –, low risk; +, moderate risk.

Table 15.3 • High-, Moderate-, and Low-Intensity Statin Therapy for Reducing the Risk of Atherosclerotic Cardiovascular Disease

	Statin Therapy[a,b]		
	High Intensity	**Moderate Intensity**	**Low Intensity**
LDL-C lowering[c,d]	≥50%	30%-49%	<30%
Statins	**Atorvastatin (40 mg**[e]**) 80 mg** **Rosuvastatin 20-40 mg**	**Atorvastatin 10 mg** (20 mg) **Rosuvastatin** (5 mg) **10 mg** **Simvastatin 20-40 mg**[f] **Pravastatin 40 mg** (80 mg) **Lovastatin 40 mg** (80 mg) Fluvastatin XL 80 mg **Fluvastatin 40 mg bid** Pitavastatin 1-4 mg	Simvastatin 10 mg **Pravastatin 10-20 mg** **Lovastatin 20 mg** Fluvastatin 20-40 mg

Abbreviations: bid, twice daily; LDL-C, low-density lipoprotein cholesterol; XL, extended release.

[a] Percent reductions are estimates from data across large populations. Individual responses to statin therapy varied in the randomized controlled trials (RCTs and should be expected to vary in clinical practice).

[b] Boldface type indicates specific statins and doses that were evaluated in RCTs, and the Cholesterol Treatment Trialists' 2010 meta-analysis. All these RCTs demonstrated a reduction in major cardiovascular events.

[c] LDL-C lowering that should occur with the dose listed below each intensity.

[d] Percent LDL-C reductions with the primary statin medications used in clinical practice (atorvastatin, rosuvastatin, and simvastatin) were estimated using the median reduction in LDL-C from the VOYAGER (an indiVidual patient data meta-analysis Of statin therapY in At-risk Groups: Effects of Rosuvastatin, atorvastatin and simvastatin) database. Reductions in LDL-C with other medications (fluvastatin, lovastatin, pitavastatin, pravastatin) were identified according to US Food and Drug Administration (FDA)–approved product labeling in adults with hyperlipidemia, primary hypercholesterolemia, and mixed dyslipidemia.

[e] Evidence from 1 RCT only; down titration if unable to tolerate atorvastatin 80 mg in the IDEAL (Incremental Decrease Through Aggressive Lipid Lowering) study.

[f] Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk of myopathy, including rhabdomyolysis.

From Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018 Nov 10. DOI: 10.1161/CIR.0000000000000624; used with permission.

Monitoring Patients

Patients should be evaluated 4 to 12 weeks after statin initiation to assess for treatment response and adverse effects. A fasting lipid panel should be rechecked. Routine measurement of hepatic enzymes or markers of muscle injury (eg, creatine kinase level) has no role unless the patient has concerning symptoms.

Management of Hypertriglyceridemia

Normal fasting triglyceride levels are less than 150 mg/dL. Triglyceride elevated levels are defined as *borderline high* (150-199 mg/dL), *high* (200-499 mg/dL), or *very high* (≥500 mg/dL).

Elevated triglyceride levels are associated with an increased risk of CVD, but it is unclear whether this association is causal. High triglyceride concentrations are also associated with other potential atherogenic abnormalities, including a low level of HDL-C, small dense LDL particles, and insulin resistance.

Pancreatitis is a rare complication of *severe* hypertriglyceridemia (usually >1,000 mg/dL). Therefore, treatment of mild to moderate hypertriglyceridemia (≤500 mg/dL), and perhaps even treatment of severe hypertriglyceridemia with levels less than 1,000 mg/dL, is mainly for CVD risk reduction and *not* for pancreatitis prevention or triglyceride lowering per se.

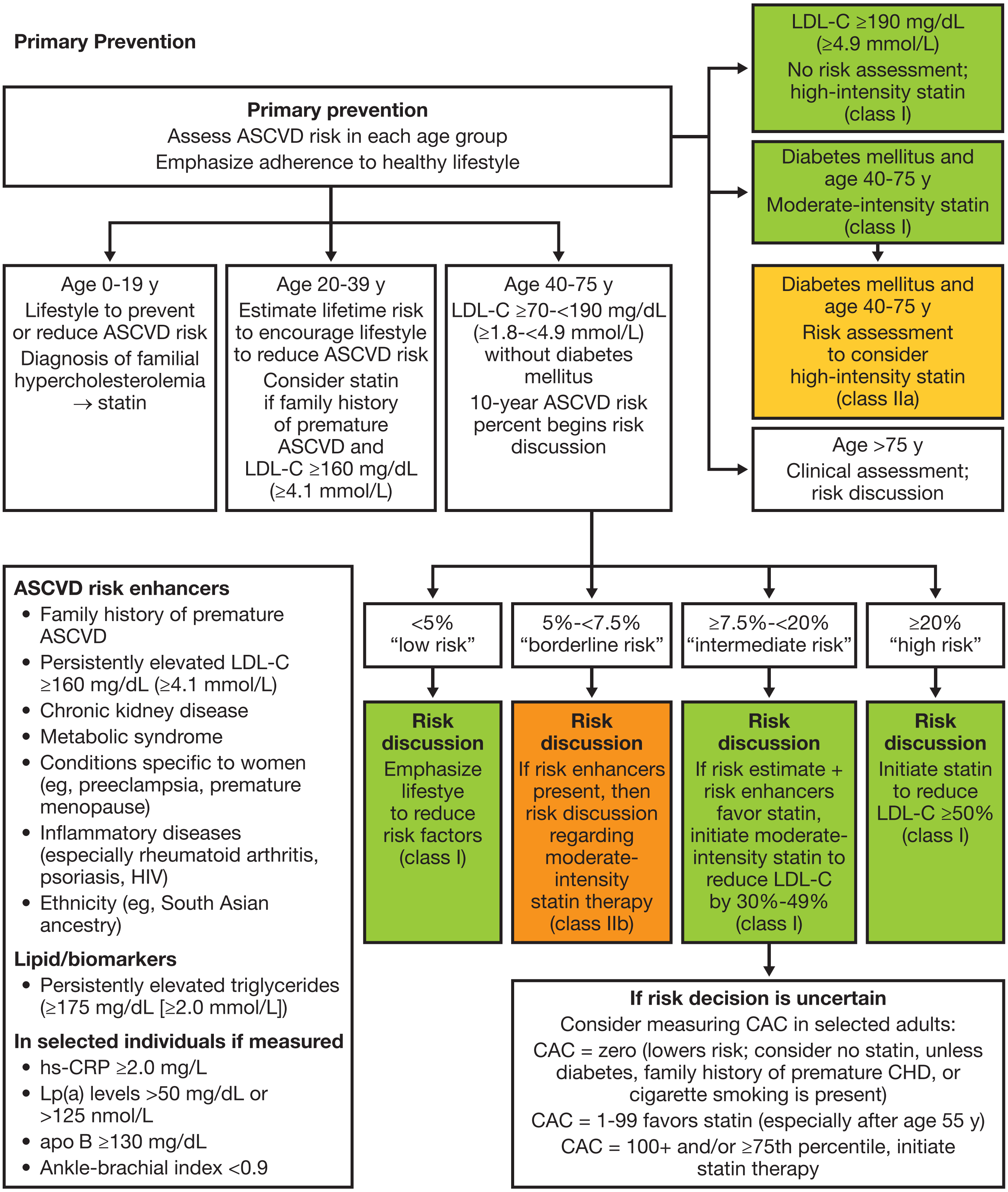
Lifestyle change is the cornerstone of management of elevated triglyceride levels. Triglyceride concentrations are exquisitely sensitive to diet and physical activity level. Consequently, limiting simple carbohydrate and alcohol intake, performing physical activity on a regular basis, and losing weight can significantly reduce triglycerides. Lowering total fat intake is necessary, however, for patients with severe hypertriglyceridemia to avoid chylomicronemia and the risk of pancreatitis. Strict glycemic control for patients with diabetes mellitus and avoidance of any medications causing hypertriglyceridemia (whenever possible) should be considered.

If a patient has persistently increased triglycerides values despite lifestyle interventions and the goal of treatment is cardiovascular risk reduction, a statin is the treatment of choice, even though it is not primarily a triglyceride-lowering medication. Statins are the only class of lipid-lowering medications that have shown consistent benefit in lowering cardiovascular morbidity and mortality rates. However, if the goal of treatment is triglyceride reduction, such as for patients with severe hypertriglyceridemia and its attendant risk of pancreatitis, patients are treated with a fibric acid derivative, nicotinic acid, or fish oil alone or in combination.

Fibric acid derivatives include gemfibrozil and fenofibrate. Gemfibrozil should be avoided in combination with a statin because of the increased chance of statin-induced myopathy. Fenofibrate is neutral from that standpoint.

Nicotinic acid may worsen glycemic control for patients with diabetes mellitus and may cause flushing, thereby limiting its tolerability. Administering aspirin 30 to 60 minutes before the patient takes nicotinic acid can minimize flushing.

The use of ω-3 fatty acids (docosahexaenoic acid and eicosapentaenoic acid) effectively reduces triglycerides at doses greater than 3 g daily. Prescription formulations are nearly 100% ω-3 fatty acids, allowing for more effective dosing than over-the-counter formulations. The main adverse effects of ω-3 fatty acids are gastrointestinal (nausea and fishy taste). Their use should be limited to patients with refractory hypertriglyceridemia.



Primary Prevention

Primary prevention
Assess ASCVD risk in each age group
Emphasize adherence to healthy lifestyle

LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; high-intensity statin (class I)

Diabetes mellitus and age 40-75 y
Moderate-intensity statin (class I)

Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin (class IIa)

Age >75 y
Clinical assessment; risk discussion

Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of familial hypercholesterolemia → statin

Age 20-39 y
Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
Consider statin if family history of premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)

Age 40-75 y
LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L) without diabetes mellitus
10-year ASCVD risk percent begins risk discussion

<5% “low risk”

Risk discussion
Emphasize lifestyle to reduce risk factors (class I)

5%-<7.5% “borderline risk”

Risk discussion
If risk enhancers present, then risk discussion regarding moderate-intensity statin therapy (class IIb)

≥7.5%-<20% “intermediate risk”

Risk discussion
If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30%-49% (class I)

≥20% “high risk”

Risk discussion
Initiate statin to reduce LDL-C ≥50% (class I)

If risk decision is uncertain
Consider measuring CAC in selected adults:
CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking is present)
CAC = 1-99 favors statin (especially after age 55 y)
CAC = 100+ and/or ≥75th percentile, initiate statin therapy

ASCVD risk enhancers
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (eg, preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (eg, South Asian ancestry)

Lipid/biomarkers
- Persistently elevated triglycerides (≥175 mg/dL [≥2.0 mmol/L])

In selected individuals if measured
- hs-CRP ≥2.0 mg/L
- Lp(a) levels >50 mg/dL or >125 nmol/L
- apo B ≥130 mg/dL
- Ankle-brachial index <0.9

Figure 15.1. *Primary Prevention of ASCVD. Color corresponds to class of recommendation in Table 2 of the original source. apo B indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CHD, coronary heart disease; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a).*

(From Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/ PCNA Guideline on the Management of Blood Cholesterol: Executive Summary. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018 Nov 10. DOI: 10.1161/CIR.0000000000000624; used with permission.)

Box 15.2 • Risk-Enhancing Factors for Clinician-Patient Risk Discussion

- Family history of premature ASCVD (men, age <55 y; women, age <65)
- Primary hypercholesterolemia (LDL-C, 160-189 mg/dL [4.1-4.8 mmol/L); non–HDL-C 190-219 mg/dL [4.9-5.6 mmol/L])[a]
- Metabolic syndrome (increased waist circumference, elevated triglyceride level [>175 mg/dL], elevated blood pressure, elevated glucose level, and low HDL-C level [>40 mg/dL in men; <50 mg/dL in women] are factors; tally of 3 makes the diagnosis)
- Chronic kidney disease (eGFR 15-59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)
- Chronic inflammatory conditions such as psoriasis, RA, or HIV/AIDS
- History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia
- High-risk race/ethnicities (eg, South Asian ancestry)
- Lipid/biomarkers: Associated with increased ASCVD risk
  - Persistently[a] elevated, primary hypertriglyceridemia (≥175 mg/dL)
  - If measured
    - Elevated high-sensitivity C-reactive protein level (≥2.0 mg/L)
    - Elevated Lp(a) level: A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a)
    - Elevated apo B level (≥130 mg/dL): A relative indication for its measurement is triglyceride level ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C value >160 mg/dL and constitutes a risk-enhancing factor
    - ABI <0.9

Abbreviations: AIDS, acquired immunodeficiency syndrome; ABI, ankle-brachial index; apo B, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); RA, rheumatoid arthritis.

[a] Optimally, 3 determinations.

From Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/ APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018 Nov 10. DOI: 10.1161/CIR.0000000000000624; used with permission.

Box 15.3 • Very High Risk[a] of Future ASCVD Events

- Major ASCVD Events
  - Recent ACS event (within the past 12 mo)
  - History of MI (other than recent ACS event listed above)
  - History of ischemic stroke
  - Symptomatic PAD (history of claudication with ABI <0.85, or previous revascularization or amputation [S4.1-39])
- High-Risk Conditions
  - Age ≥65 y
  - Heterozygous familial hypercholesterolemia
  - History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
  - Diabetes mellitus
  - Hypertension
  - CKD (eGFR, 15-59 mL/min/1.73 m^2) (S4.1-15, S4.1-17)
  - Current smoking
  - Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
  - History of congestive HF

Abbreviations: ABI, ankle-brachial index; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral arterial disease.

[a] Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

From Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/ APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018 Nov 10. DOI: 10.1161/CIR.0000000000000624; used with permission.

Secondary Prevention in Patients With Clinical ASCVD

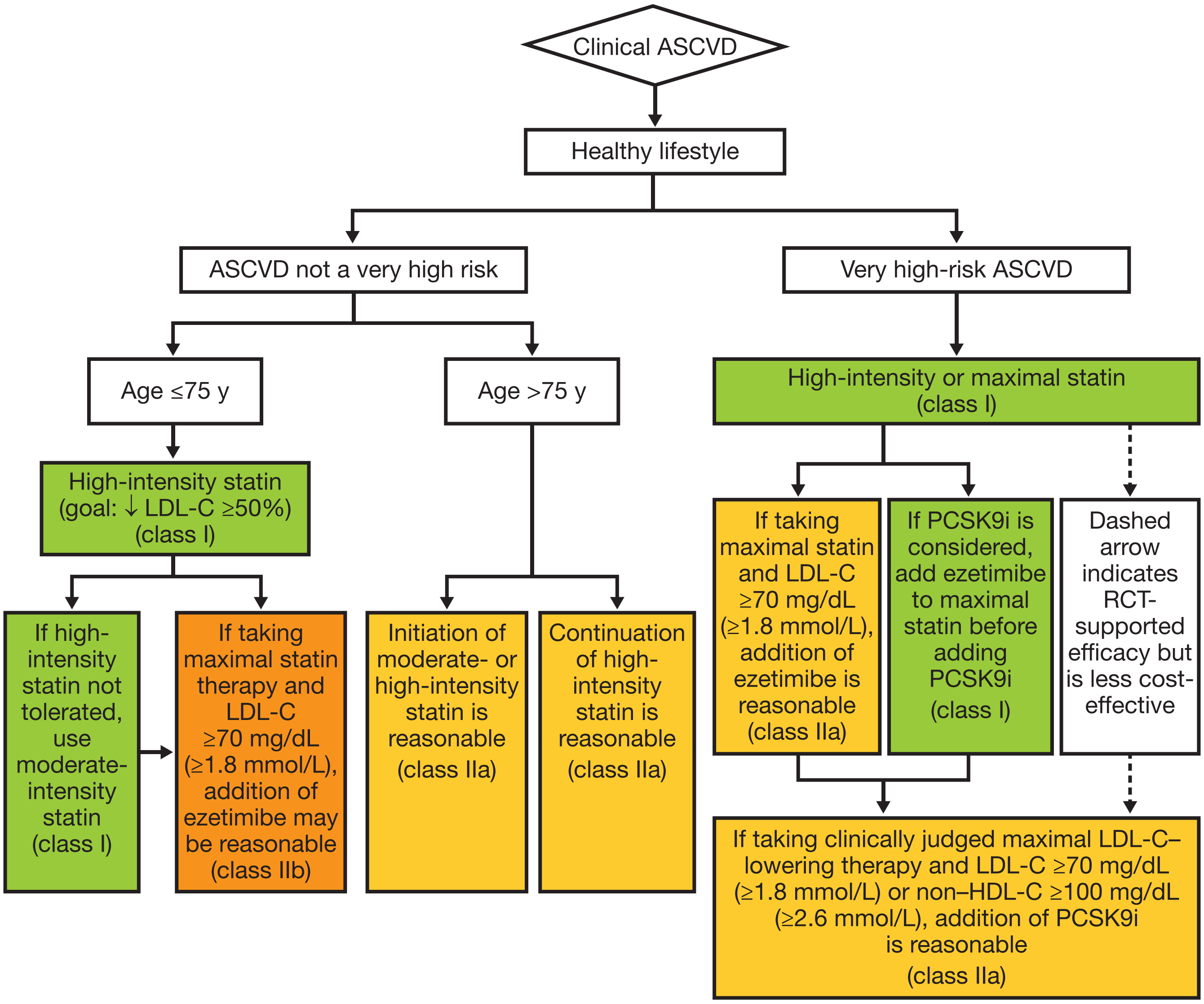

Clinical ASCVD
Healthy lifestyle
ASCVD not a very high risk
Very high-risk ASCVD
Age ≤75 y
Age >75 y
High-intensity or maximal statin (class I)
High-intensity statin (goal: ↓ LDL-C ≥50%) (class I)
If taking maximal statin and LDL-C ≥70 mg/dL (≥1.8 mmol/L), addition of ezetimibe is reasonable (class IIa)
If PCSK9i is considered, add ezetimibe to maximal statin before adding PCSK9i (class I)
Dashed arrow indicates RCT-supported efficacy but is less cost-effective
If high-intensity statin not tolerated, use moderate-intensity statin (class I)
If taking maximal statin therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), addition of ezetimibe may be reasonable (class IIb)
Initiation of moderate- or high-intensity statin is reasonable (class IIa)
Continuation of high-intensity statin is reasonable (class IIa)
If taking clinically judged maximal LDL-C–lowering therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L) or non–HDL-C ≥100 mg/dL (≥2.6 mmol/L), addition of PCSK9i is reasonable (class IIa)

Figure 15.2. *Secondary Prevention in Patients With Clinical ASCVD. Color corresponds to class of recommendation in Table 2 of the original source. Clinical ASCVD consists of acute coronary syndrome; those with history of myocardial infarction, unstable angina, or other coronary arterial revascularization; stroke; transient ischemic attack; or peripheral artery disease, including aortic aneurysm, all of atherosclerotic origin. Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (Table 4 in the original source). ASCVD indicates atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCSK9i, PCSK9 inhibitor; RCT, randomized controlled trial.*

(From Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/ APhA/ ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018 Nov 10. DOI: 10.1161/CIR.0000000000000624; used with permission.)

Management of Low HDL-C Level

The latest ACC/AHA guidelines on cholesterol reduction for ASCVD risk reduction do not recommend specific medical therapy for patients with low HDL-C levels per se. Statin therapy is indicated for such patients if they meet any of the criteria for treatment, as previously discussed in this chapter. Studies have not shown any cardiovascular benefit with the use of specific therapies for increasing HDL-C levels, including nicotinic acid and fibric acid derivatives.

Lifestyle changes, including exercise, weight loss (for overweight patients), substitution of monounsaturated fatty acids for saturated fatty acids, and smoking cessation can raise HDL-C levels. Drugs causing low HDL-C levels should be discontinued whenever possible.

KEY FACTS

- ✓ Recommend therapeutic lifestyle changes—healthy diet, exercise, weight management, and smoking cessation to *all* patients with elevated CVD risk
- ✓ Key to managing elevated triglyceride levels—lifestyle changes
- ✓ Severe hypertriglyceridemia—need to decrease total fat intake

16 Obesity and Nutritional Disorders

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Obesity

Etiologic Factors

The prevalence of overweight and obesity has been increasing in the United States and the westernized world. The cause of the recent obesity epidemic involves a complex interplay between genetic and environmental factors. Specific, rare genetic disruptions of the hypothalamic regulation of energy homeostasis pathways can cause obesity (eg, Prader-Willi syndrome). However, most cases of obesity result from a group of gene variants exposed to environmental factors. The 2 major environmental factors that contribute to overweight and obesity are excess caloric intake and low physical activity. Additional risk factors include smoking cessation, sleep deprivation, contributory social networks, lower socioeconomic status, medications, and, less commonly, health conditions.

Health Risk Assessment

Body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) is used to assess the health risk of body weight. Waist circumference (WC), another variable used to predict health risk, is a surrogate for visceral fat. WC is most useful for persons who have a BMI between 25 and 35. Individuals who have an increased BMI in combination with an increased WC, which indicates excess visceral fat, have a greater health risk than if the BMI alone is increased. BMI values greater than 35 are associated with high health risk, so in that BMI range, WC is less meaningful (Table 16.1).

Overweight (BMI 25.0-29.9) and **obesity** (BMI ≥30.0) are associated with increased morbidity and mortality risk (Box 16.1). Some of the increased mortality risk may be negated by cardiovascular fitness. Screening for weight-related medical complications is indicated for patients who are overweight or obese (measurement of blood pressure, fasting blood glucose or hemoglobin A_{1c}, lipid profile, and thyrotropin and evaluation for obstructive sleep apnea).

Key Definitions

Overweight: *Body mass index 25.0-29.9.*

Obesity: *Body mass index ≥30.0.*

Obesity Management

Implementation of healthy lifestyle changes is the key factor to managing overweight and obesity. Dietary changes with caloric restriction (by 250-500 kcal daily) are required for weight loss. Macronutrient composition has minimal impact on weight loss at 12 months. Regular physical activity promotes weight loss by creating an additional caloric deficit but is insufficient alone. However, regular physical activity is a key determinant to maintaining weight loss.

Achieving a weight loss goal of 5% to 10% of initial body weight is associated with multiple benefits, including prevention of type 2 diabetes mellitus and cardiovascular benefits. Predictors of weight loss success include having a greater initial body weight, engaging in more minutes of physical activity weekly, recording caloric intake, and participating in group behavioral therapy. Considerable weight loss occurs with aggressive dietary restriction (very low-calorie diets of <800 kcal daily) and bariatric surgery, but with very low-calorie diets, the prevalence of weight regain is high.

Medications for Weight Loss

Use of medication improves the likelihood of losing 5% to 10% of initial body weight. The 5 medications approved by the US Food and Drug Administration (FDA) for obesity

Table 16.1 • BMI, Waist Circumference, and Health Risk

			Health Risk	
BMI	**BMI Classification**	**Waist Circumference, cm**	**BMI Alone**	**BMI With Waist Circumference**
<18.5	Underweight			
18.5-24.9	Normal			
25.0-29.9	Overweight		Increased	
		Women: >88		High
		Men: >102		High
30.0-34.9	Class I obesity		High	
		Women: >88		Very high
		Men: >102		Very high
35.0-39.9	Class II obesity		Very high	
≥40.0	Class III obesity		Extremely high	

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

From National Institutes of Health, National Heart, Lung, and Blood Institute, North American Association for the Study of Obesity. The practical guide: identification, evaluation, and treatment of overweight and obesity in adults. Bethesda (MD): National Institutes of Health; c2000. NIH Publication No. 00-4084.

are phentermine alone (for short-term use [<12 weeks]) and in combination with topiramate in extended-release formulation, orlistat, lorcaserin, bupropion/naltrexone combination, and liraglutide (Table 16.2). Medications are generally reserved for patients who are obese or overweight and have at least 1 obesity-associated comorbidity.

Phentermine is a sympathomimetic agent that suppresses appetite, but few long-term studies (>12 weeks) have been performed, and there are insufficient data detailing efficacy and safety. Phentermine has not been implicated in the development of cardiac valve abnormalities and pulmonary hypertension. Patients previously treated with fenfluramine or dexfenfluramine should be evaluated for cardiac valve abnormalities. Sibutramine was removed from the market after it was reported to increase the risk of nonfatal heart attacks and stroke in a high-risk population.

Box 16.1 • Health Risks Associated With Obesity

Type 2 diabetes mellitus
Hypertriglyceridemia
Hypertension
Obstructive sleep apnea
Coronary artery disease
Congestive heart failure
Atrial fibrillation
Thromboembolic disease
Degenerative joint disease
Gastroesophageal reflux disease
Nonalcoholic steatohepatitis
Cancer
Death

Orlistat is a lipase inhibitor that limits dietary fat absorption. Administered with a low-fat diet (fat <30% of calories), it is associated with greater weight loss than placebo. Its main adverse effects involve the gastrointestinal tract; diarrhea and flatulence often limit adherence to therapy. A daily multivitamin is recommended to prevent vitamin deficiencies. Concurrent use with medications influenced by fat absorption (eg, cyclosporine, amiodarone, warfarin) can limit the efficacy of those drugs.

Lorcaserin is a selective serotonin receptor agonist that can lead to satiety, hypophagia, and subsequent weight loss. In combination with a hypocaloric diet, lorcaserin was associated with greater weight loss than placebo in several large studies. Participants receiving lorcaserin did not have the valvular abnormalities that were identified in patients receiving other nonselective serotonin agonists (fenfluramine and dexfenfluramine). Lorcaserin use can lead to serotonin syndrome, especially when combined with medications that increase serotonin levels.

Phentermine-topiramate extended-release capsules combine 2 medications known to lead to weight loss. The weight loss mechanism for topiramate is not known, but, similar to lorcaserin, topiramate in combination with a hypocaloric diet was associated with greater weight loss than placebo in several large studies. Phentermine-topiramate extended-release capsules are contraindicated in pregnancy because of the risk of cleft lip and cleft palate.

Table 16.2 • Approved Pharmacologic Agents for the Treatment of Obesity

Drug	Mechanism	Contraindications	Common Adverse Effects
Phentermine	Sympathomimetic	Pregnancy, breastfeeding, glaucoma, hyperthyroidism, use of MAOI within 14 days, history of cardiovascular disease	Insomnia, tremor, headache, risk of dependency, palpitations, elevated blood pressure
Orlistat	Pancreatic lipase inhibitor	Pregnancy, cholestasis, chronic malabsorption syndromes	Abdominal pain, bloating, diarrhea, acute pancreatitis, renal failure
Lorcaserin	Selective serotonin 2C receptor agonist	Pregnancy	Headache, back pain, nasopharyngitis, nausea, dizziness
Phentermine-topiramate ER	Sympathomimetic and anticonvulsant	Pregnancy, breastfeeding, glaucoma, hyperthyroidism, use of MAOI within 14 days, history of cardiovascular disease	Dizziness, dry mouth, constipation, depression, insomnia, tremor, headache, risk of dependency, palpitations, elevated blood pressure
Bupropion/naltrexone SR	Dopamine and norepinephrine reuptake inhibitor/opioid receptor antagonist	Pregnancy, uncontrolled hypertension, history of seizures, bulimia or anorexia, use of MAOI within 14 days	Nausea, constipation, headache, vomiting, insomnia, dizziness, dry mouth, diarrhea
Liraglutide	GLP-1 agonist	Pregnancy, family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2	Nausea, diarrhea, vomiting, headache, dyspepsia, dizziness, abdominal pain

Abbreviations: ER, extended release; GLP-1, glucagonlike peptide-1; MAOI, monoamine oxidase inhibitor; SR, sustained release.

Similarly, bupropion/naltrexone sustained release combines 2 medications with weight loss properties. Bupropion is a dopamine/norepinephrine reuptake inhibitor approved for depression and smoking cessation. Naltrexone is an opioid receptor agonist approved for opioid dependency. The 2 drugs work synergistically to suppress appetite through the proopiomelanocortin neurons in the arcuate nucleus. The main adverse effects tend to be insomnia, dizziness, dry mouth, and change in mood. Bupropion/naltrexone sustained release is contraindicated in pregnancy and for patients with uncontrolled hypertension or history of seizure disorder. It also cannot be taken within 14 days of use of monoamine oxidase inhibitors.

Liraglutide is a glucagonlike peptide-1 (GLP-1) analogue and previously has been approved for treatment of type 2 diabetes mellitus at doses of up to 1.8 mg per day. In addition to its metabolic properties, liraglutide suppresses appetite, increases satiety, and delays gastric emptying, leading to recent approval by the FDA for weight loss indication with doses up to 3.0 mg per day. The main adverse effects involve the gastrointestinal tract, such as nausea or diarrhea. Liraglutide is also contraindicated in pregnancy or for persons with a family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.

Bariatric Surgery

The indications for bariatric surgery are 1) BMI greater than or equal to 40 *or* 2) BMI greater than or equal to 35 *and* weight-related medical comorbidities, documented efforts at medically supervised weight management, absence of psychologic contraindications, and life expectancy of more than 5 years.

Mechanisms for weight loss are variable after bariatric surgery (Box 16.2). The most commonly performed operations are the Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG). Both of these procedures are mainly performed laparoscopically, which decreases postoperative pain and minimizes wound complications. Bariatric surgery has shown its beneficial effects on obesity-associated comorbidities, including prevention and resolution of type 2 diabetes mellitus. Resolution rates have been reported for other long-term medical problems, including obstructive sleep apnea, gastroesophageal reflux disease, hypertriglyceridemia, and hypertension.

Restrictive operations for obesity, such as bariatric procedures, are generally associated with less weight loss and lower resolution rates for most obesity-related complications. Biliopancreatic diversion with a duodenal switch (BPD-DS) is associated with the greatest reported weight loss and the greatest effect on the complications of excess weight. The use of BPD-DS

Box 16.2 • Mechanisms for Weight Loss After Bariatric Surgery

Dietary restriction—sleeve gastrectomy, vertical banded gastroplasty, and laparoscopic adjustable gastric banding

Malabsorptive—biliopancreatic diversion with a duodenal switch

Combination of restriction and malabsorptive—Roux-en-Y gastric bypass is mostly limited because of its higher complication rate than RYGB and SG.

Early Complications of Bariatric Surgery

Reported perioperative mortality rate with bariatric surgery is less than 1%. The most common cause of death is pulmonary embolism. Anastomotic leak with subsequent peritonitis is the second most common cause of death with RYGB and BPD-DS. Gastric staple-line leak, stricture, and bleeding are the most common complications from SG. Although it does not have an anastomosis procedure, SG does carry a risk of a leak due to the long stomach staple line and increased intraluminal pressure. A high level of awareness is critical when assessing an ill patient presenting with dyspnea or abdominal pain within weeks after a bariatric operation. Sinus tachycardia is the most common physical finding in patients with an anastomotic or staple-line leak. Risk factors associated with higher perioperative morbidity and mortality rates are male sex, age more than 60 years, BMI greater than 60, smoking, untreated obstructive sleep apnea, inactivity, and surgeon inexperience.

Other anastomotic complications can occur after RYGB or SG. Anastomotic ulcerations and stricture of the gastrojejunal anastomosis are the most common following RYGB. Risk factors include use of nonsteroidal anti-inflammatory drugs, prior *Helicobacter pylori* infection, and smoking. Strictures can occur along any portion of the GS staple line and can be caused by a twisting or hematomas along the line. Presenting symptoms of ulcerations or strictures can include epigastric pain with or without nausea and vomiting. Esophagogastroduodenoscopy is the diagnostic study of choice; balloon dilation of a stricture can be performed. Anastomotic ulcers are effectively treated with proton pump inhibitors with or without sucralfate.

Nutrition After Bariatric Surgery

Nutritional deficiencies are recognized complications of bariatric surgery. Therefore, empirical vitamin supplementation is recommended for all patients after the operation and should include vitamin B$_{12}$, a multivitamin, and calcium with vitamin D.

After any bariatric procedure, acute thiamine deficiency can occur in a patient who is vomiting and cannot maintain adequate oral intake. In addition to gastrointestinal tract symptoms, neurologic concerns are common. Because Wernicke-Korsakoff syndrome may occur, thiamine must be supplemented before intravenous infusion of dextrose-containing fluids.

Anemia is the most common manifestation of deficiencies of iron, vitamin B$_{12}$, or folate; it resolves with appropriate supplementation. Iron deficiency anemia is the most common nutritional deficiency reported, especially among menstruating women, and may require intravenous infusion of iron. Folate and vitamin B$_{12}$ deficiencies are less common as a result of empirical vitamin supplementation, but a high level of awareness is needed because of the variable adherence to supplementation regimens. Neurologic complications due to vitamin B$_{12}$ deficiency may not resolve. Low vitamin B$_{12}$ levels should be confirmed with a methylmalonic acid level. Care must be taken to assess folate status before supplementation. Measurement of the ferritin level is a reliable screening test for iron deficiency.

Inadequate diet, inadequate supplementation, and often, persistent gastrointestinal tract symptoms such as diarrhea can lead to long-term nutritional deficiencies. Vitamin D deficiency is common among obese patients seeking bariatric surgery and may worsen during rapid weight loss after the operation. Hypocalcemia is a late finding and is often absent in mild or moderate deficiencies. The most common early findings may be increased parameters of bone turnover (elevated bone alkaline phosphatase level) and secondary hyperparathyroidism (elevated parathyroid hormone level). Secondary hyperparathyroidism is also influenced by decreased dietary calcium. The only way to detect calcium deficiency early is by identifying hypocalciuria in a 24-hour urine collection. Long-term vitamin D deficiency can lead to metabolic bone disease with low bone mineral density or mineralization defects (or both), resulting in osteomalacia. Deficiencies of other fat-soluble vitamins besides vitamin D (ie, vitamins A, E, and K) are less common but may occur. Protein malnutrition is a worrisome complication of BPD-DS and must be reversed in 1% to 2% of patients who have had the procedure.

KEY FACTS

✓ Medications may be used in combination with lifestyle changes to treat obesity

✓ Obese patients can gain cardiovascular benefits from losing as little as 5% of their initial weight

✓ Vitamin deficiencies—a risk for patients after bariatric surgery

✓ Confirmation of low vitamin B$_{12}$ level—high methylmalonic acid level

Late Complications of Bariatric Surgery

After bariatric surgery, cholelithiasis develops in one-third of patients; in 40% of these patients, it becomes symptomatic. Prophylactic cholecystectomy was commonly performed at bariatric surgery when it was an open abdominal operation (before the laparoscopic approach became common). Administration of ursodeoxycholic acid for 6 months after surgery decreases the prevalence of gallstone development and is gaining popular use. Therefore, prophylactic cholecystectomy is no longer indicated.

Bacterial overgrowth in the gastrointestinal tract is common after RYGB and BPD-DS. Abdominal pain and bloating associated with diarrhea are common symptoms. Esophagogastroduodenoscopy with small-bowel aspirates for culture or breath tests is usually diagnostic. When bacterial overgrowth is suspected or confirmed, antibiotic therapy should be instituted; various regimens are available. Resolution of symptoms occurs within 1 week. Bacterial overgrowth can recur, worsening the malabsorption of nutrients and increasing the risk of vitamin deficiencies.

Other complications include renal stone disease (primarily calcium oxalate stones). Fat malabsorption and lack of dietary calcium allow increased absorption of intestinal oxalate, increasing the risk of calcium oxalate stone formation. Insulin-mediated hypoglycemia may occur in patients who have postprandial symptoms that suggest hypoglycemia. Symptoms may be difficult to differentiate from those of classic dumping syndrome. Further evaluation requires documentation of hypoglycemia (blood glucose <55 mg/dL), endogenous hyperinsulinemia (insulin >3 mcIU/mL; C peptide >0.2 ng/mL), and a negative sulfonylurea screen while the patient is symptomatic.

Nutrition

Ideal weight is reflected by BMI values of 18.5 to 24.9. Persons with BMI values less than 18.5 are considered underweight, and the risk of morbidity and death increases with BMI values less than 15.

An optimal diet should provide the caloric requirements to maintain the weight within an ideal BMI range and minimize the risk of illness. A high intake of fruits and vegetables has been consistently shown to provide multiple health benefits, particularly in lowering the risk of cardiovascular disease (Box 16.3).

Micronutrient Supplementation

Multivitamin supplementation has not been shown to provide health benefits to the US population at large, and it is recommended only for persons not meeting their nutritional needs orally owing to illness or self-imposed dietary restriction. The benefits of empirical vitamin supplementation have been reported for folic acid in women of childbearing age (to prevent neural tube defects) and for vitamin D (to prevent metabolic bone disease).

Empirical supplementation of antioxidant vitamins (β-carotene and vitamin E) to prevent cardiovascular disease is no longer advised because of both a lack of benefit and the potential risk of lung cancer in smokers and patients who have a history of asbestos exposure. Folic acid supplementation to decrease homocysteine levels is no longer advised owing to a lack of benefit in preventing cardiovascular disease.

Supplementation with ω-3 fatty acids (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]) lowers cardiovascular mortality risk. Eating at least 1 serving of a fatty fish (rich in ω-3 fatty acids) weekly or supplementing with DHA and EPA is beneficial, with studies suggesting that antiarrhythmic properties contribute to a lower risk of cardiovascular death. Increased doses of ω-3 fatty acids lower triglyceride levels.

Box 16.3 • Daily Dietary Guidelines to Decrease the Risk of Cardiovascular Disease in Obesity

- Restrict dietary protein to <20% of total calories
- Prefer lean meats
- Restrict dietary fat to <35% of total calories
- Avoid *trans* fats
- Restrict saturated fats to <10% of total calories
- Restrict dietary cholesterol to <300 mg daily
- Prefer polyunsaturated fats
- Restrict dietary carbohydrates to <55% of total calories
- Prefer fruits, vegetables, and whole grains
- Restrict the intake of refined carbohydrates, processed grains, and starches

Micronutrient Deficiencies

In the general US population, nutritional deficiencies of calcium, vitamin D, vitamin B_{12}, and iron are common. Current dietary intake of dairy products and other food sources of calcium is low. Recommended calcium intake varies by age, and calcium supplementation is effective. Various calcium preparations are available. Calcium carbonate requires gastric acid for optimal absorption, so dosing is advised with meals; efficacy may be lower with medications that decrease gastric acid secretion. Calcium citrate is generally better absorbed than calcium carbonate, and it is preferred if a patient has a gastrointestinal tract illness.

Vitamin D deficiency is associated with decreased sun exposure, inflammatory bowel disease, and renal disease. Vitamin D status is reflected by 25-hydroxyvitamin D levels (reference range, 20-50 ng/mL). Mild to moderate deficiencies (10-20 ng/mL) are common, are often asymptomatic, and can be associated with secondary hyperparathyroidism. Severe deficiency (<10 ng/mL) increases the risk of bone mineralization defects and osteomalacia. Patients with severe vitamin D deficiency often report deep bone pain and proximal muscle weakness.

Deficiencies of vitamin D and the other fat-soluble vitamins A, E, and K occur in patients with inflammatory bowel disease, short-bowel syndrome, bariatric surgery, or other malabsorption disease states. Deficiency of vitamin A (retinol) can lead to night blindness or xerophthalmia. Vitamin E deficiency is rare, but it can lead to neuromuscular disease with clinical manifestations, including ataxia, decreased proprioceptive and vibratory sensations, and hyporeflexia. Clinical signs of vitamin K deficiency include easy bruising, mucosal bleeding, and any other symptoms of abnormal coagulation.

The cause of vitamin B_{12} deficiency can be 1) autoimmune (eg, pernicious anemia, which is characterized by the presence of anti–parietal cell antibodies); 2) gastrointestinal tract disease that impairs vitamin B_{12} absorption (eg, inflammatory bowel disease, any gastrointestinal tract surgery or illness affecting the gastric antrum or ileum); or 3) medications (eg, metformin). A low vitamin B_{12} level (<100 ng/L) is consistent with a deficiency. Low-normal values should be evaluated with a methylmalonic acid measurement; a deficiency is indicated by an elevated methylmalonic acid level. Macrocytic anemia is the most common presenting abnormality. Neurologic symptoms can occur and may not fully resolve if identification and supplementation are delayed. Patients with vitamin B_{12} deficiency should receive parenteral supplementation, particularly if they have neurologic symptoms or if the underlying cause is abnormal gastrointestinal tract absorption. Vitamin B_{12} levels should be monitored until they are in the reference range. To maintain adequate levels, vitamin B_{12} can be administered orally or parenterally. Folate levels should be checked before supplementing vitamin B_{12}.

Iron deficiency is another common micronutrient deficiency, and it is the most common abnormality in patients with celiac sprue. Other persons at risk include those with self-imposed dietary restrictions (including vegetarians and vegans), patients who have gastrointestinal tract illness or have had surgery affecting the duodenum (where most iron is absorbed), and women with heavy menses. Oral supplementation is sufficient unless more aggressive treatment with packed cell transfusion is needed or the patient has intolerance to oral iron.

Zinc and copper deficiencies can occur in patients with long-term parenteral nutrition, bariatric surgery, or malabsorptive diseases. Signs and symptoms of zinc deficiency include dysgeusia, alopecia, impaired wound healing, and dermatitis. Signs of copper deficiency include ataxia, neuropathy, anemia, and neutropenia. Patients with niacin deficiency can present with glossitis, dermatitis, dementia, and diarrhea.

Nutritional Support

Nutritional assessment of critically ill patients should be performed on admission to the intensive care unit. Ideally, nutritional needs are calculated with an accurate body weight, which is often difficult to measure if the patient is critically ill. Protein needs are greater in critically ill patients, but caution must be taken when patients have comorbidities contraindicating a high-protein load (eg, renal insufficiency, liver disease).

If adequate oral intake can be resumed within 7 days, previously healthy patients generally do not benefit from nutritional support. Intravenous fluid hydration is adequate for most patients in an uncomplicated hospital setting. The potential need for nutritional support should be considered for critically ill patients and for patients with a BMI less than 18.5, a loss of 5% of initial body weight in 1 month, a loss of 10% of initial body weight in 6 months, more than 7 days of not meeting nutritional needs, or multiple organ failure.

Enteral feedings (delivered into the stomach with a nasogastric tube or as postpyloric feedings) are preferred unless contraindicated. Absolute contraindications include complete intestinal obstruction, acute ischemia, or acute peritonitis. Patients who benefit include perioperative patients with chronic liver disease, critically ill patients, and malnourished geriatric patients. Enteral feedings also reduce the risk of sepsis.

Gastric feedings should be avoided in clinical settings that may promote intolerance or potential complications, including any conditions that impair gastric emptying or increase the risk of aspiration. Most medications can be provided by this route.

Patients with contraindications or intolerance to gastric feedings or concerns with potential complications from gastric feeding should receive postpyloric feedings. Fewer medications can be safely administered by this route.

Parenteral nutrition is advised for patients who do not meet their nutritional needs for 7 days and have contraindications or intolerance to enteral feedings. Parenteral nutrition is associated with risks that include infection and hyperglycemia, and patients must be monitored appropriately.

Hyperglycemia is the most common complication for patients receiving parenteral nutrition, and glucose monitoring is advised. Hypertriglyceridemia is a recognized complication; limiting the calories provided as fat is advised for patients with triglyceride levels greater than 300 mg/dL. An increased risk of bloodstream infection (bacterial and fungal organisms) is associated with parenteral nutrition. For patients receiving parenteral nutrition, the risk of fungal infection is up to 5-fold greater. Common risk factors include poor hygiene in managing venous access and formula, severe illness, and increased duration of catheter insertion.

Refeeding syndrome is a recognized complication of aggressive nutritional support in the clinical setting of malnutrition. Major risk factors include BMI less than 16, unintentional weight loss greater than 15% in the past 3 to 6 months, little nutritional intake for more than 10 days, and low levels of potassium or phosphate before a feeding session. Abnormalities due to hyperinsulinemia occur in response to feedings and include hypokalemia, hypophosphatemia, hypomagnesemia, volume overload, and edema, with hypophosphatemia being very common. Severe hypophosphatemia is associated with heart failure, arrhythmias, impaired diaphragmatic contractility, liver function test abnormalities, delirium, and seizures. Patients at risk for refeeding syndrome must be identified so the necessary precautions can be taken. Prevention includes gradual caloric progression, monitoring of clinical status, and frequent monitoring for and correction of electrolyte abnormalities identified before the initiation of nutritional support.

KEY FACTS

- ✓ Iron deficiency anemia—common in patients with celiac sprue
- ✓ Copper deficiency—mimics neurologic signs of vitamin B_{12} deficiency
- ✓ Major complications of parental nutrition—hyperglycemia, central line infections, liver disease, and vitamin deficiencies
- ✓ Hypophosphatemia—a common sign of refeeding syndrome

17 Pituitary Disorders

PANKAJ SHAH, MD

Hypopituitarism

Etiologic Factors

Hypopituitarism usually results from a deficiency of anterior pituitary hormones or, rarely, from tissue resistance to these hormones. Deficiency may be from primary pituitary disease, pituitary stalk disorders, hypothalamic disease, or an extrasellar disorder impinging on, or infiltrating, the hypothalamic-pituitary unit.

Primary pituitary disease results from the loss of anterior pituitary cells and may be congenital or acquired. Common causes are pituitary tumors and their surgical or radiotherapeutic ablation. Infrequent causes include pituitary infarction (eg, postpartum pituitary necrosis, also known as *Sheehan syndrome*), pituitary apoplexy, lymphocytic hypophysitis, infiltrative diseases (eg, hemochromatosis), and metastatic disease (eg, from breast or lung).

Hypothalamic hypopituitarism results from hypothalamic or pituitary stalk disease associated with the loss of hypophysiotropic regulatory hormones of the anterior pituitary cells. Primary hypothalamic diseases are relatively rare and include disorders that are genetic (Kallmann syndrome); traumatic (accidental, surgical, or radiotherapeutic); inflammatory or infiltrative (eg, tuberculosis, sarcoidosis, histiocytosis X); vascular (eg, bleeding disorders, vasculitis); or neoplastic, including primary neoplasms (eg, glioma, ependymoma, hamartoma, gangliocytoma) and metastatic neoplasms.

Functional hypothalamic disorders are common (Box 17.1). Structural abnormalities are not evident on imaging, and normal endocrine function is ultimately restored after the cause is managed or removed.

Extrasellar disorders impinge on and impair the function of the hypothalamic-pituitary unit. Examples include craniopharyngioma (most common), optic glioma, meningioma, nasopharyngeal carcinoma, sphenoid sinus mucocele, and carotid artery aneurysms.

Clinical Features

Patients with hypopituitarism can present with features of deficiency of 1 or more of the anterior pituitary hormones. The clinical picture depends on age at onset, hormones affected, extent and duration of deficiency, and acuteness of the process. The most common presentation is that of a long-term process of insidious onset.

Chronic Illness

Gonadotropin Deficiency

The features of gonadotropin deficiency are from deficiency of sex hormones and diminished fertility. Women may have infertility, oligomenorrhea or amenorrhea, loss of libido, vaginal dryness and dyspareunia, involution of the uterus and genitalia, and atrophy of breasts. Male patients may have loss of libido, erectile dysfunction, infertility, atrophy or loss of secondary sex characteristics, atrophy of the testes and prostate, and, occasionally, gynecomastia. In both sexes, fine wrinkling of the skin may be seen radially around the mouth or eyes, and osteoporosis may occur.

Corticotropin Deficiency

The features of corticotropin (ACTH) deficiency result primarily from a lack of cortisol. These features include malaise, anorexia, weight loss, gastrointestinal tract disturbances, musculoskeletal aches and pains, hypoglycemia, hyponatremia, susceptibility to adrenocortical crises, pallor, an inability to tan or maintain a tan, and a loss of skin pigmentation. The characteristics of mineralocorticoid deficiency are absent because aldosterone secretion depends on the renin-angiotensin system, not on ACTH; therefore, hyperkalemia and hypovolemia with orthostatism are typically absent. Partial ACTH deficiency may cause symptoms only during periods of acute medical or surgical illness, when elevated cortisol levels are needed.

Box 17.1 • Functional Hypothalamic Disorders and Related Causes

Functional suppression of gonadotropin-releasing hormone (GnRH)—weight disorders, exercise, psychiatric disorders, systemic disease, or endocrinopathy (eg, hyperprolactinemia, thyroid or adrenal disorders, severely uncontrolled diabetes mellitus)

Functional lack of growth hormone (GH)—emotional deprivation syndrome

Functional lack of corticotropin (ACTH)—withdrawal of prolonged supraphysiologic glucocorticoid therapy

Functional lack of thyrotropin—correction of a hyperthyroid state (first few weeks)

Thyrotropin Deficiency

Thyrotropin deficiency results in a lack of thyroid hormones (triiodothyronine [T_3] and thyroxine [T_4]) and the characteristic features of slowing of emotional, mental, and physical functions. The thyroid gland is atrophic.

Prolactin Deficiency

Postpartum women who have prolactin deficiency cannot lactate. Prolactin deficiency does not cause other symptoms in women or men.

Growth Hormone Deficiency

The characteristics of growth hormone (GH) deficiency in adults are nonspecific and include asthenia, fatigue, muscle weakness, osteopenia, obesity, psychosocial difficulties, and increased cardiovascular risk.

Acute Illness

Adrenocortical crises may be precipitated by various events (Box 17.2). Manifestations of acute pituitary deficiency include fasting hypoglycemia (decreased hepatic glucose release due to lack of cortisol and GH); hyponatremic syndrome (decreased free water clearance with cortisol and thyroxine deficiency, renal water conservation due to decreased glomerular filtration rate and unchecked secretion of antidiuretic hormone [ADH]—the syndrome of inappropriate secretion of ADH [SIADH]); and increased sensitivity to central nervous system depressants (decreased metabolism and clearance due to lack of cortisol and thyroid hormones).

Box 17.2 • Causes of Adrenocortical Crises

Withdrawal of prolonged glucocorticoid therapy without proper glucocorticoid coverage during recovery of the hypothalamic-pituitary-adrenal axis

Pituitary surgery without optimal glucocorticoid stress coverage

Acute medical or surgical illness in a patient who has a lack of cortisol that is unrecognized or poorly managed

Pituitary apoplexy

Thyroid hormone replacement therapy in a patient who has an associated and unrecognized deficiency of corticotropin

Diagnosis

Diagnosis of hypopituitarism requires documentation of hypopituitarism *and* identification of the cause. For deficiencies of tropic hormones (eg, thyrotropin, ACTH, luteinizing hormone [LH], follicle-stimulating hormone [FSH], and GH), target gland function is evaluated (Table 17.1).

Gonadotropin Axis

Male patients with hypopituitarism have a low morning serum testosterone concentration, inappropriately “normal” or low serum LH and FSH levels, and a low sperm count. Female patients have a low serum estradiol level and inappropriately normal or low serum LH and FSH levels.

ACTH Axis

In the appropriate clinical setting, a morning cortisol value less than 3 mcg/dL strongly indicates adrenocortical failure. In an unstressed ambulatory patient with a serum cortisol concentration greater than 10 mcg/dL, cortisol deficiency is unlikely, and a value greater than 18 mcg/dL excludes the diagnosis. If values are 3 to 10 mcg/dL, a provocative test should be used to assess adrenal function. Provocative tests may also be performed if clinical suspicion of glucocorticoid insufficiency is strong and the morning cortisol level is between 10 and 18 mcg/dL. Twenty-four–hour urinary cortisol concentration is physiologically low and has no role in the diagnosis of cortisol deficiency.

In chronic ACTH deficiency, the adrenal cortices are atrophic and do not secrete cortisol in response to the short-acting exogenous ACTH stimulation test (ie, the cosyntropin test). Adrenocortical failure is confirmed by the absence of an increased serum ACTH level and the absence of a cortisol response to exogenous ACTH stimulation.

In a patient with recent-onset cortisol deficiency caused by a lack of ACTH from pituitary destruction (eg, from a postoperative cause, postpartum hemorrhage, apoplexy), exogenous ACTH may stimulate cortisol production and produce a falsely reassuring test result despite glucocorticoid insufficiency.

Thyrotropin Axis

A low serum free T_4 level and an inappropriately normal or low serum thyrotropin level support the diagnosis of central hypothyroidism. In contrast, thyrotropin concentrations are high in patients with primary hypothyroidism.

Growth Hormone

GH deficiency is likely present in a patient with demonstrable structural disease of the pituitary gland. A low age-specific

Table 17.1 • Clinical Manifestations and Tests for Pituitary Hormone Deficiencies

Hormone	Manifestation	Test
Thyrotropin	Usually asymptomatic. Cold intolerance, decreased appetite, dry skin, constipation, bradycardia, hyponatremia, depression	Free thyroxine level
ACTH	Malaise, lack of appetite, weight loss, nausea or vomiting, hyponatremia, hypoglycemia Women: decreased pubic and axillary hair	Morning cortisol level ACTH stimulation test
LH and FSH	Hypogonadism and infertility Men: decreased libido, erectile dysfunction, lack of energy, loss of pubic and axillary hair Women: amenorrhea, vaginal dryness, dyspareunia Men and women: fine wrinkles lateral to eyes and mouth	Men: sperm count—if normal, hypogonadism is ruled out; if abnormal, measurement of morning testosterone is needed (total testosterone with or without bioavailable or free testosterone) Women: menstruation—if regular, hypogonadism is ruled out; if irregular, measurement of estradiol is needed
GH	Nonspecific symptoms: lack of energy, muscle weakness, asthenia, fatigue, osteopenia, obesity, psychosocial difficulties, hypoglycemia	GH and IGF-1 Dynamic tests (arginine infusion or insulin hypoglycemia) are infrequently performed to confirm diagnosis and meet insurance needs
Prolactin	Failure to lactate	Testing for prolactin is rarely required
ADH	Polyuria, hypernatremia	24-h urine volume Serum and urine osmolality

Abbreviations: ACTH, corticotropin; ADH, antidiuretic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; IGF-1, insulinlike growth factor 1; LH, luteinizing hormone.

serum level of insulinlike growth factor 1 (IGF-1) is a good screening test. In the absence of other pituitary hormone deficiencies, a provocative test is indicated if treatment with GHs is contemplated. The preferred test uses arginine in combination with GH-releasing hormone (GHRH). The insulin hypoglycemia test is performed with appropriate precautions; it is contraindicated in patients who have seizures or cerebrovascular or cardiovascular disease.

Prolactin

Tests for prolactin deficiency are rarely, if ever, needed in clinical practice.

Radiologic Evaluation

Radiologic evaluation includes imaging of the hypothalamic-pituitary region by magnetic resonance imaging (MRI) or computed tomography (CT) and, in the presence of suprasellar disease, neuro-ophthalmologic evaluation to assess visual fields, visual acuity, and optic discs. MRI is preferred.

In determination of the cause of hypopituitarism, suspected functional causes must be removed or corrected. Normalization of pituitary function after correction of a functional cause lends support to “functional” hypopituitarism. If the functional causes are excluded or if hypopituitarism persists despite removal or correction of a functional cause, evaluation for structural hypothalamic-pituitary disease is mandatory. This evaluation is based on the clinical setting and appropriate endocrine and anatomical studies.

Therapy

Therapy for hypopituitarism includes correction of the cause and, when applicable, administration of the hormones of the target glands or, in selected cases, of pituitary hormones.

ACTH Deficiency

For ACTH deficiency, glucocorticoid replacement is critical. Patients need instruction about dose modification during acute illness. For patients with deficiencies of both ACTH and thyrotropin, glucocorticoid therapy should be initiated *before* thyroid hormone therapy to avoid a thyroid hormone–induced increased need for cortisol and precipitation of an acute adrenocortical crisis. Adequacy of therapy is judged by clinical criteria, symptom resolution, and the absence of signs and symptoms of supraphysiologic replacement. Serum ACTH levels cannot be used to assess adequacy of therapy.

The usual replacement dose of glucocorticoids is prednisone 4 to 7.5 mg in 1 or 2 doses or hydrocortisone 15 to 40 mg in 2 or 3 doses. The morning dose is taken soon after awakening, and the evening dose is taken in the afternoon. Mineralocorticoid replacement is not needed in glucocorticoid deficiency due to ACTH deficiency.

Thyrotropin Deficiency

For thyrotropin deficiency, the drug of choice is levothyroxine. The adequacy of therapy should be assessed through the patient’s feeling of well-being and the serum level of free T_4 in the mid- to upper-normal range. The serum thyrotropin level should not be used to monitor the adequacy of the levothyroxine dose adjustment in hypothyroidism caused by thyrotropin deficiency.

Gonadotropin Deficiency

Gonadotropin deficiency is treated with sex steroids. In female patients, estrogen therapy is used. Progestogens must be used for patients with an intact uterus. Birth control pills often provide adequate hormone replacement.

In male patients, testosterone can be given in the form of periodic injections, a transdermal gel or patch, or an inserted testosterone pellet. The status of the prostate in middle-aged and elderly men should be assessed before beginning therapy and recheck the status annually. If the testosterone concentration is in the goal range and the patient reports no symptomatic benefits, testosterone treatment is often withdrawn.

For restoration of fertility, FSH and LH therapy (or gonadotropin-releasing hormone therapy in patients with hypothalamic disorders and an intact pituitary) may be indicated. The patient's psychosexual needs and lifestyle should be evaluated to assess the effect of therapy.

GH Deficiency

For GH deficiency, short-term GH therapy increases muscle strength and improves body composition. It may also improve exercise capacity, bone mineral density, cardiac function, and sense of well-being. GH therapy is considered for patients with symptoms of GH deficiency, especially when organic hypothalamic-pituitary disease is present. The goal of therapy is to restore the serum IGF-1 level to the reference range and to avoid adverse effects. If the IGF-1 concentration is in the goal range and the patient finds no symptomatic benefits, GH treatment is withdrawn. The long-term effects of such therapy are unknown; thus, a benefit-risk profile cannot be determined.

KEY FACTS

- ✓ Hypopituitarism—usually from a deficiency of anterior pituitary hormones
- ✓ Diagnosis of hypopituitarism—the cause needs to be documented in addition to documenting the presence of hypopituitarism
- ✓ Glucocorticoid (cortisol) deficiency should be corrected before correcting other hormone deficiencies

Pituitary Tumors

Pituitary tumors can be described by size, as microadenomas (≤10 mm) or macroadenomas (>10 mm); by extent, as sellar or sellar and extrasellar; and by type, as functioning or nonfunctioning. These are almost always benign tumors. **Functioning pituitary tumors** include prolactinomas (40%-50%), GH-producing tumors (10%-15%), ACTH-producing tumors (10%-15%), and thyrotropin-producing tumors (<5%). **Nonfunctioning pituitary tumors** (30%-40%) include the gonadotropin-producing tumors, tumors that make subunits (but not full hormones), and null-cell adenomas. Pituitary tumors are usually sporadic; rarely, they may be part of disorders such as multiple endocrine neoplasia type 1 (MEN-1), McCune-Albright syndrome, or Carney complex.

Key Definitions

Functioning pituitary tumors: *prolactinomas, growth hormone–producing tumors, corticotropin-producing tumors, and thyrotropin-producing tumors.*

Nonfunctioning pituitary tumors: *gonadotropin-producing tumors, tumors that make hormone subunits, and null-cell adenomas.*

Clinical Features

The usual manifestation of a pituitary tumor is that of a chronic, slowly evolving disorder. The clinical characteristics of pituitary tumors result from 3 components: 1) mass effect on surrounding structures; 2) hormone deficiency or excess caused by the mass effect; and 3) hormone excess from the tumor cells (Box 17.3). Rarely, pituitary tumors manifest acutely with pituitary apoplexy (acute hemorrhage into the pituitary gland), which may be the first clinical expression of the underlying tumor.

Diagnosis

The presence of a pituitary tumor is suggested by its clinical characteristics and confirmed by pituitary imaging. MRI is the preferred imaging technique. Neuro-ophthalmologic evaluation is important, particularly if suprasellar extension is present. Endocrine evaluation includes evaluation for hormonal excess or deficiency and for the presence of MEN-1. A pituitary tumor is diagnosed if a sellar mass is associated with an excess of anterior pituitary hormone (except for mild hyperprolactinemia, which can occur with nonpituitary masses and the "stalk effect"). Otherwise, the diagnosis is confirmed at surgical exploration.

Treatment

Dopamine agonists are often used as sole management for prolactinomas. Pituitary surgery is required for prolactinoma if the prolactin is not responding to dopamine agonists or the patient cannot tolerate these agents. All other pituitary tumors are primarily treated with surgery. The conservative management approach of observation is an option for small tumors that have no effect on the quality or quantity of a patient's life, especially when the patient's expected lifespan is not long.

Transsphenoidal surgery is the operation of choice for most pituitary tumors; the transcranial approach is used when a large

Box 17.3 • Clinical Features of Pituitary Tumors

- Mass effects (headaches and evidence of tumor extension beyond the confines of the sella)
  - Superior tumor extension
    - Chiasma syndrome—impaired visual acuity and visual field defects
    - Hypothalamic syndrome—vegetative disturbance in thirst, appetite, satiety, sleep, and temperature regulation with diabetes insipidus or SIADH
    - Obstructive hydrocephalus
    - Frontal lobe dysfunction
  - Lateral tumor extension
    - Impairment of cranial nerves III, IV, V, and VI; may result in diplopia, facial pain, and temporal lobe dysfunction
  - Inferior tumor extension
    - Nasopharyngeal mass
    - Cerebrospinal fluid rhinorrhea
- Endocrine effects
  - Hypersecretory states
    - Gigantism or acromegaly (uncontrolled production of growth hormone)
    - Hyperprolactinemia (prolactin excess from interruption of the stalk or from prolactin produced by the tumor cells)
    - Cushing disease and Nelson-Salassa syndrome (corticotropin excess before and after adrenalectomy)
    - Thyrotoxicosis (thyrotropin excess), less often
    - Luteinizing hormone or FSH excess, usually clinically silent
  - Hypopituitarism
    - Caused by tumor growth that destroys the pituitary gland
  - Endocrine associations
    - MEN-1 (ie, parathyroid tumor or hyperplasia [primary hyperparathyroidism])
    - Endocrine pancreas tumor or hyperplasia (Zollinger-Ellison syndrome, hypoglycemia, or watery diarrhea)
    - Rarely, other endocrine gland tumors (thyroid or adrenal) and lipomas

Abbreviations: FSH, follicle-stimulating hormone; MEN-1, multiple endocrine neoplasia type 1; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

suprasellar tumor extension is present. Surgical morbidity and mortality rates and the available neurosurgical expertise should be considered. The rate of morbidity (eg, bleeding, infection, transient diabetes insipidus [DI], cerebrospinal fluid rhinorrhea) is less than 1% with microadenomas and less than 4% with macroadenomas; mortality rate is less than 1% with an experienced surgeon. Persistence or recurrence of the tumor is less than 20% to 30% for microadenomas and 50% to 70% for macroadenomas.

Options with radiotherapy include external beam radiotherapy and Gamma Knife (Elekta AB) stereotactic radiosurgery. However, radiotherapy results in a long latent period (a few months to years) before benefits are realized and in postradiotherapy hypopituitarism (in 10 years in >50% of patients or in a smaller percentage with Gamma Knife therapy). Central nervous system damage and the development of central nervous system tumors are rare.

Somatostatin analogues are used as adjuncts for the management of GH- or thyrotropin-producing tumors. Pegvisomant, a GH-receptor blocker, is used to block the harmful metabolic effects of excess GH in the management of GH-producing tumors refractory to other management options.

Follow-up is essential to monitor for persistence or recurrence of the tumor, development of hypopituitarism in patients treated with surgery or radiotherapy, and the possible occurrence of MEN-1 in familial cases.

Prolactinoma and the Hyperprolactinemic Syndrome

Pituitary tumors associated with hyperprolactinemia may be prolactinomas, mixed tumors (eg, GH- and prolactin-producing tumors), or nonfunctioning tumors with suprasellar extension and the stalk effect. In hyperprolactinemia from stalk effect, impingement of the mass on the pituitary stalk interferes with the access of hypothalamic dopamine to the anterior pituitary and results in disinhibition of prolactin secretion by normal lactotrophs.

Clinical Features

Mass effects include hypopituitarism and expressions of extrasellar extension of the pituitary tumor. Persons with hyperprolactinemia, especially men, may be asymptomatic; women of childbearing age often present with symptoms early.

In women, hyperprolactinemia is usually expressed as galactorrhea, ovulatory and menstrual dysfunction (short luteal phase or anovulation leading to infertility), oligomenorrhea or amenorrhea, hypogonadism, and decreased libido. In some women, hyperprolactinemia may be associated with hirsutism and acne.

In men, hyperprolactinemia results in hypogonadism, infertility due to oligospermia, and, rarely, galactorrhea or gynecomastia. Hyperprolactinemia is frequently unrecognized in men because decreased libido and impaired potency may be dismissed as aging or attributed to psychological factors. In men with a pituitary tumor, marked hyperprolactinemia and a macroadenoma are common at presentation.

Diagnosis

Prolactinoma must be distinguished from other causes of hyperprolactinemia and from other pituitary area masses. Hyperprolactinemia can be physiologic or pathologic in origin.

Physiologic hyperprolactinemia may occur in pregnancy and the postpartum state and in conditions of physical stress, such as surgery or acute illness. All women of reproductive age should have a pregnancy test performed if physiologic hyperprolactinemia is a possibility.

Pathologic hyperprolactinemia may occur with primary hypothyroidism. Thyrotropin should be checked in all patients being evaluated for hyperprolactinemia. Pathologic hyperprolactinemia may also occur in patients with primary pituitary disease or hypothalamic or stalk disease and result in the loss of dopaminergic disinhibition of prolactin secretion by normal lactotrophs. Causes of primary pituitary disease include prolactinoma, so-called mixed tumors, nonfunctioning pituitary tumors with suprasellar extension and stalk-effect hyperprolactinemia, hypophysitis, and primary empty sella.

Hypothalamic or stalk disorders can be functional or organic. *Functional hypothalamic disorders* lead to hyperprolactinemia because of interference with the synthesis, secretion, or action of dopamine or other hypothalamic regulators of prolactin secretion. These disorders may be caused by drugs (eg, neuroleptics, antidepressants, narcotics, estrogens); primary hypothyroidism (15%-30%); chest wall irritative lesions (eg, herpes zoster, dermatitis, thoracotomy) and nipple stimulation (eg, during sexual activity); renal failure; and cirrhosis or hepatic encephalopathy.

Organic hypothalamic disorders include traumatic disorders (eg, from an operation or radiotherapy), inflammatory disorders (eg, from sarcoidosis or histiocytosis X), or neoplastic disorders (eg, from craniopharyngioma, optic glioma, meningioma, or metastases such as those from the breast or lungs). Ectopic hyperprolactinemia from a malignancy is very rare.

The diagnosis of prolactinoma is established with elevated serum levels of prolactin, usually greater than 10 times the upper limit of the reference range. However, prolactinomas, particularly microprolactinomas, may be associated with prolactin levels that exceed the upper limit of the reference range but by less than 10 times.

If the prolactin level is less than 10 times the upper limit of the reference range, functional causes should be ruled out. If a functional cause is suspected, reevaluation after addressing it is appropriate. If hyperprolactinemia does not resolve in about 3 months, the patient should be evaluated for hypothalamic-pituitary disease. If a functional cause is not suspected, organic hypothalamic-pituitary disease should be ascertained by imaging the hypothalamic-pituitary region, preferably with MRI. Other pituitary functions and the visual fields are evaluated, if appropriate, for the presence of tumor and the closeness of the tumor to the optic nerve, optic chiasm, and optic tracts. MRI should be performed only after ruling out or addressing a functional cause of hyperprolactinemia, especially if the prolactin level is less than 10 times the upper limit of the reference range.

If a cause is not found, the hyperprolactinemia is considered to be of indeterminate origin. Follow-up evaluation may show evidence of a mass. The serum level of prolactin should be checked every 6 to 12 months, and imaging should be repeated in 1 to 2 years, or sooner if new symptoms develop.

Differential Diagnosis

Increased prolactin concentrations may be caused by macroprolactin in blood. Macroprolactin, measured as prolactin in prolactin assays, is an immunoglobulin-linked prolactin that is biologically inert. Macroprolactin is suspected as a cause of excess prolactin when prolactin levels are high in patients with no symptoms, functional cause, or pituitary-hypothalamic disorder that could indicate hyperprolactinemia. The blood is then tested for macroprolactin concentrations.

Treatment

Not every person who has a high prolactin level needs to be treated to normalize prolactin concentrations. If a person has a microadenoma causing hyperprolactinemia or idiopathic hyperprolactinemia, treatment is indicated if hyperprolactinemia is thought to be causing infertility, hypogonadism, or socially significant galactorrhea (ie, spontaneous galactorrhea that stains clothes). Dopamine agonist therapy is first-line therapy. Transsphenoidal pituitary surgery is rarely needed for a microprolactinoma, but it is needed if dopamine agonists are not effective or not tolerated and if therapy for hyperprolactinemia is considered necessary. If hypogonadism is the indication for therapy and the patient's fertility does not need to be preserved, estrogen therapy may be used instead to prevent the adverse effects of hypogonadism in women (eg, bone loss, vaginal dryness). If none of the indications for therapy are present, patients may be observed without therapy and with a check of serum prolactin annually and follow-up imaging every 2 to 3 years.

Macroprolactinoma

Therapy is indicated for all patients who have a large pituitary tumor (≥1 cm) that is making prolactin. These large tumors pose a dual threat: a mass lesion and the effects of hyperprolactinemia. Drug therapy with a dopamine agonist is the preferred treatment. Surgical excision or radiotherapy is reserved for patients with drug intolerance or drug resistance (10%-20% of patients receiving bromocriptine; 3%-7%, cabergoline).

Dopamine Agonists

Dopamine agonists are the mainstay of prolactinoma therapy. They suppress prolactin secretion and proliferation of prolactin-producing cells, restore gonadal function (in 70%-80% of patients), and decrease tumor size (in >50% of patients). Monitoring for cardiac valve disease is not indicated for patients receiving smaller doses of dopamine agonists for hyperprolactinemia. Therapy with dopamine agonists is temporizing in most patients with macroadenoma, and discontinuation usually leads to recurrence of tumor growth and endocrine dysfunction. However, in some patients who have the outcomes of normoprolactinemia and significantly smaller tumor, use of the drug can be withdrawn after 1 to 2 years. In these patients, the tumor may have a long remission but needs long-term monitoring.

Dopamine agonist therapy should be stopped if pregnancy is confirmed. In pregnancy, the risk of microprolactinoma growth is less than 5%, and the risk of macroprolactinoma growth is 20% to 40%. Patients are observed closely; if tumor growth is suspected, imaging (without gadolinium during pregnancy) should be performed. If clinically significant tumor growth complicates pregnancy, surgical excision or reinstitution of dopamine agonist therapy is considered.

Surgical Treatment of Prolactinomas

For microadenomas, the surgical cure rates are 60% to 80%; for macroadenomas, 0% to 30%.

KEY FACTS

- ✓ Pituitary tumors—microadenomas (≤10 mm) or macroadenomas (>10 mm); sellar or both sellar and extrasellar; functioning or nonfunctioning
- ✓ Pituitary tumor mass effect—on surrounding structures (eg, optic chiasm) or on the normal pituitary, pituitary stalk, and hypothalamus (eg, ACTH deficiency and prolactin excess)
- ✓ Pituitary tumors may produce excess hormone (eg, prolactinoma and GH-producing tumor)

GH Tumors: Acromegaly and Gigantism

Etiologic Factors

Acromegaly is nearly always caused by a GH-producing pituitary tumor. These tumors usually secrete only GH; infrequently, they may simultaneously secrete prolactin, the α-subunit of glycoprotein hormones (LH, FSH, and thyrotropin), or ACTH. Rarely, acromegaly may be caused by ectopic GHRH-producing tumors (hypothalamic or ectopic). Very infrequently, it can be caused by ectopic GH-producing tumors.

GH-producing pituitary tumors are usually sporadic. Rarely, they are familial and may occur in association with MEN-1, McCune-Albright syndrome, or Carney complex.

Clinical Features

The clinical features of GH tumors are related to excess levels of GH and IGF-1 and to the mass effect of the pituitary tumor on the pituitary and surrounding structures. Excess levels of GH and IGF-1 lead to tall stature (gigantism) in childhood and to characteristic acromegalic features in adults (Box 17.4). Pituitary mass–related manifestations include hypopituitarism, stalk-effect hyperprolactinemia, and anatomical effects related to the extrasellar extension of a macroadenoma.

Box 17.4 • Clinical Features of Growth Hormone Tumors

Bone and soft-tissue overgrowth, with coarsening of facial features; frontal bossing; prognathism; widened spaces between teeth; macroglossia; increased hat, glove, ring, or shoe size; acroparesthesias; and nerve entrapment syndromes

Hyperhidrosis, heat intolerance, skin tags, and increased skin oiliness

Carbohydrate intolerance (20%); rarely, frank diabetes mellitus, hypercalciuria, and hyperphosphatemia; and urolithiasis

Fibromas or acanthosis nigricans

Sleep apnea (obstructive and central)

Cardiovascular effects, including hypertension, left ventricular hypertrophy, diastolic dysfunction, cardiomyopathy, arrhythmias, and coronary artery disease

Propensity to early and severe degenerative joint disease

Compared with survival among age-matched controls, survival among patients with untreated or poorly treated acromegaly is reduced by an average of 10 years (excess mortality risk primarily results from cardiovascular, cerebrovascular, and respiratory deaths). Patients with acromegaly have a 2- to 3-fold increased risk of cancer and a 3- to 8-fold increased risk of colon cancer and premalignant colon polyps.

Endocrine Diagnosis

Serum IGF-1 provides the best screening test for the diagnosis of acromegaly. Age- and sex-matched serum IGF-1 levels are almost universally increased. (IGF-1 levels are normally increased in pregnancy and in adolescence.) The diagnosis is confirmed by the demonstration of abnormal GH suppressibility within 1 to 2 hours after a 75-g glucose load (failure of GH suppression to <1 ng/mL or a paradoxical increase in GH secretion). A random serum level of GH is not helpful because of the pulsatile nature of GH secretion.

Radiologic Diagnosis

When the diagnosis is documented biochemically, imaging of the sella is indicated. MRI is the study of choice. If a pituitary tumor is not delineated (a rare event) or if a symmetrical pituitary enlargement is suggestive of hyperplasia, serum GHRH levels are measured to exclude a GHRH-producing tumor. If the GHRH level is high, a search is made for evidence of an ectopic GHRH-producing tumor. Evidence of an ectopic GH-producing tumor is sought when both the pituitary imaging findings and the GHRH level are normal.

Therapy

Because of the increased morbidity and mortality risk associated with untreated acromegaly, active treatment is indicated for all patients. Optimal therapy is directed at normalization of GH and IGF-1 levels, preservation or normalization of pituitary functions, and control of comorbidities with an aim to reduce excess mortality risk from increased GH. No single line of treatment can accomplish all these goals in all patients. Often, several forms of therapy are needed for patients with acromegaly.

All patients with acromegaly should be screened for hypertension, diabetes mellitus, cardiovascular disease, osteoarthritis, and sleep apnea. Colonoscopy should be performed to exclude colon polyps.

Ectopic GH or GHRH Tumors

Surgical resection is the therapy of choice for ectopic GH or GHRH tumors. For persistent or incurable disease, pharmacotherapy is considered.

ACTH-Producing Tumors

ACTH-producing tumors are discussed in Chapter 14 (“Gonadal and Adrenal Disorders”).

Gonadotropin-Producing Tumors

Gonadotropin-producing tumors constitute the largest fraction of nonfunctioning pituitary tumors. Although more than 80% of them can synthesize the gonadotropins or their subunits, increased serum levels of FSH, LH, or their subunits are found in less than 35% of affected patients. Clinically, the tumors are macroadenomas at presentation; patients may present at any age, but they are usually middle-aged or elderly men. Extrasellar effects dominate the clinical picture, and some degree of hypopituitarism is usually present. The tumor mass may be associated with stalk-effect hyperprolactinemia. Imaging (MRI or CT) usually shows the sellar mass with extrasellar extension. Currently, no effective medical therapy is available. Treatment is usually surgical, with or without postoperative radiotherapy. Endocrine replacement therapy is given for the management of hypopituitarism.

Thyrotropin-Producing Tumors

The characteristic clinical presentations of patients who have primary thyrotropin tumors are diffuse goiter and hyperthyroidism. Other presentations include extrasellar mass effects and deficiency of other pituitary hormones. Laboratory testing indicates the presence of a thyrotropin-producing tumor in a thyrotoxic patient if the thyrotropin value is normal or increased with elevated thyroid hormone levels. Unlike Graves disease, thyrotropin-producing tumors occur with equal frequency in both sexes without causing ophthalmopathy and dermopathy. Sometimes, it is difficult to distinguish thyrotropin-induced hyperthyroidism from T_4-resistance syndromes. Thyrotropin-producing tumors may have elevated α-glycoprotein subunit levels, and the thyrotropin response to thyrotropin-releasing hormone is absent. MRI or CT shows a sellar mass with or without extrasellar extension.

Treatment options for thyrotropin-producing tumor include ablation (surgically or with irradiation), pharmacologic therapy with the somatostatin analogue octreotide, and ancillary measures for the management of thyrotoxicosis.

Pituitary Incidentalomas

Pituitary incidentalomas are relatively common. Autopsy studies suggest that 10% to 20% of persons harbor small pituitary tumors. CT or MRI of the head performed for nonendocrine reasons shows mass lesions in the sella larger than 3 mm in 4% to 20% of persons. Potential threats to health from these incidentalomas include functioning pituitary tumors and incidentalomas with actual or potential mass effects. Masses larger than 10 mm are more likely to be associated with mass effects (hypopituitarism, hyperprolactinemia from a stalk effect, or chiasma syndrome) and are more likely to enlarge during observation.

The diagnostic approach includes assessing pituitary function and mass effects. Assessing for functioning pituitary tumors may include the overnight 1-mg dexamethasone suppression test or 24-hour urinary free cortisol test and measurement of prolactin, IGF-1, free T_4 and thyrotropin, and FSH, LH, and their subunits. In the asymptomatic patient, only a serum prolactin level is measured. The other pituitary hormones are assessed only when suspicion is supported by clinical findings.

Active intervention is dictated by finding a functioning pituitary tumor that can cause morbidity or death (ie, all functioning pituitary tumors except a small microprolactinoma in a postmenopausal female patient) or identifying an incidentaloma larger than 1 cm in diameter with extrasellar extension. Otherwise, the patient is observed, and imaging studies are repeated in 6 to 12 months and then later at less frequent intervals. An increase in the size of the nonfunctioning incidentaloma under observation requires surgical intervention.

Miscellaneous Pituitary Disorders

Craniopharyngioma

Craniopharyngioma is a slow-growing, encapsulated squamous cell tumor originating from remnants of the Rathke pouch. It is the most common tumor in the pituitary region in childhood but can occur at any age. Two-thirds of the tumors are suprasellar; one-third originate in or extend into the sella. Most are cystic, and some are solid or mixed. These tumors have a propensity to calcify. The clinical presentation includes obstructive hydrocephalus, hypothalamic syndrome (DI and hyperprolactinemia), chiasmal defects, hypopituitarism, or calcification in or around the sella, as seen incidentally on radiography. Radiography shows calcification in intrasellar or suprasellar regions (75% of children and 25% of adults). CT or MRI shows a solid or cystic mass, calcification (on CT), and low attenuation values (cholesterol content).

Surgical excision is possible for only small craniopharyngiomas. Larger craniopharyngiomas are surgically decompressed. A ventriculoperitoneal shunt is used for obstructive hydrocephalus. Other treatments include postoperative radiotherapy and management of endocrine dysfunction.

Key Definition

Craniopharyngioma: *a slow-growing, encapsulated squamous cell tumor originating from Rathke pouch remnants.*

Pituitary Apoplexy

Pituitary apoplexy refers to hemorrhagic infarction of the pituitary gland with or without underlying disease. The usual clinical setting is that of a pituitary tumor, irradiated pituitary tumor, pregnancy, postpartum state, anticoagulation therapy, increased intracranial pressure, vascular disease (eg, diabetes mellitus), or vasculitis (eg, temporal arteritis). Persons are asymptomatic if the bleeding is small or gradual. In the acute condition, hemorrhage is often sudden or large, with severe headache, ophthalmoplegia, visual defects, meningismus, depressed sensorium, and acute adrenocortical crisis leading to death if unrecognized and untreated. The diagnosis is made on the basis of the characteristic clinical, radiologic, and surgical findings. Therapy includes neurosurgical decompression and hormonal support. Late sequelae may include hypopituitarism, secondary empty sella syndrome, and regression of hypersecretory syndrome in an infarcted functioning pituitary tumor.

Key Definition

Pituitary apoplexy: *hemorrhagic infarction of the pituitary gland, with or without underlying disease.*

Sheehan Syndrome

Pituitary infarction in a patient with massive postpartum hemorrhage leads to panhypopituitarism, including failure of lactation and deficiencies of glucocorticoids, thyroid hormone, and sex hormones. This condition is called **Sheehan syndrome**. Early recognition and hormone replacement therapy are central to preventing the disabling adverse effects of hypopituitarism.

Key Definition

Sheehan syndrome: *panhypopituitarism from pituitary infarction with massive postpartum hemorrhage.*

Lymphocytic Hypophysitis

Lymphocytic hypophysitis is presumed to be of autoimmune origin. It usually occurs in association with other autoimmune endocrinopathies and affects adults, predominantly women and especially during pregnancy and the postpartum period. The clinical presentation may include hypopituitarism or the presence of a sellar mass associated with hyperprolactinemia. The main differential diagnoses are prolactinoma and Sheehan syndrome. The diagnosis depends on the associations and the results of surgical exploration. No specific therapy is available. Hormonal replacement is given as needed.

ADH Deficiency: Diabetes Insipidus

Etiologic Factors

Renal water output is dependent on the presence of a good concentration of arginine vasopressin (ADH) and a responsive distal nephron. Therefore, DI with excessive water loss may result from decreased responsiveness of the distal nephron to ADH (nephrogenic or vasopressin-resistant DI) or from decreased ADH secretion (central DI).

Hypothalamic, or Central, DI

Hypothalamic, or central, DI may result rarely from genetic or more commonly from acquired disorders of the anterior hypothalamus, median eminence, or upper pituitary stalk. Genetic disorders are rare. Causes of acquired disorders include trauma (closed head trauma or neurosurgery); inflammatory or granulomatous disorders (sarcoidosis, tuberculosis, or histiocytosis X); primary neoplasms such as craniopharyngioma, germinoma, and optic glioma; and metastatic neoplasms, primarily from the breast or lung. Idiopathic hypothalamic DI is probably the most common cause of the syndrome and may be an autoimmune disorder.

Dipsogenic DI

Dipsogenic DI may be idiopathic or associated with psychosis or, rarely, organic disorders of the anterior hypothalamus such as sarcoidosis or neoplasms.

Nephrogenic DI

Nephrogenic DI, or decreased responsiveness of the distal nephron to ADH, may also be caused by genetic or acquired disorders. The most common causes are chronic renal disease, electrolyte abnormalities (hypercalcemia or hypokalemia), and ADH-antagonist drugs such as lithium and demeclocycline.

Clinical Features

Polyuria and polydipsia, often with a preference for ice-cold water, are characteristic of patients with DI. Nocturia is usually present, and enuresis may be the presenting sign with children. An abrupt onset of symptoms usually points to central DI. Absence of nocturia, variable intensity or intermittency of symptoms, and a 24-hour urine output greater than 18 L suggest primary polydipsia.

DI leads to dehydration if the patient cannot drink enough water to compensate for the inability of the kidneys to concentrate urine and preserve body water. This may occur if the patient is unconscious for any reason, cannot obtain fluids, or has an impaired thirst mechanism. In such circumstances, extreme hyperosmolar dehydration and hypertonic encephalopathy may develop. Other clinical manifestations include those of DI and the etiologic disorder.

Endocrine Diagnosis

In patients with polyuria and dilute urine, the diagnosis of DI depends on the random measurement of plasma osmolality (serum sodium is a good surrogate) and urine osmolality levels under conditions of unrestricted fluid intake. The induction of plasma hyperosmolality (either by water deprivation or by administration of hypertonic saline) is used to assess the patient's ability to produce ADH and to respond to it. The patient's response can be assessed 1) indirectly with measurements of urine volume and osmolality before and after fluid restriction or ADH administration (or both) or 2) directly with measurements of plasma levels of ADH in addition to plasma and urine osmolalities.

Although the diagnosis of severe DI from any cause can be straightforward, the diagnosis is challenging when patients have partial DI. Moreover, prolonged periods of polyuria, regardless of the primary cause, may decrease the renal urine-concentrating ability (renal medullary washout), in effect adding a nephrogenic DI component to the basic disease process.

In a patient with polyuria and dilute urine, a random plasma osmolality greater than 295 mOsm/kg points to neurogenic or nephrogenic DI. These can be differentiated by the response to exogenous ADH. In an untreated patient with polyuria, a random plasma osmolality less than 280 mOsm/kg indicates primary polydipsia.

Etiologic Diagnosis

Clinical evidence of hypothalamic-pituitary or systemic disorders is sought, and visual fields and anterior pituitary functions are evaluated. MRI is performed to look for structural abnormalities in the hypothalamic-pituitary region. The most common causes of central DI are idiopathic DI, trauma (accidental or neurosurgical), metastases from breast or lung cancer, and tumors in the hypothalamic area. Systemic diseases with hypothalamic or stalk involvement must be considered. Disorders involving the stalk may be congenital (ectopic neurohypophysis and Rathke cleft cyst), inflammatory (neurosarcoidosis, Langerhans cell histiocytosis, and lymphocytic hypophysitis), or neoplastic (craniopharyngioma, pituitary adenoma, metastatic disease, germinoma, and astrocytoma).

Therapy

Whenever possible, therapy for DI is directed at the cause. For mild central DI, free access to water may be all that is needed. Desmopressin is used for moderate to severe central DI, with the first aim being to ensure control of nocturnal polyuria and disturbed sleep. For nephrogenic DI, thiazides are the only treatment available.

KEY FACTS

- ✓ Hyperprolactinemia treatment—not indicated unless the patient has infertility, hypogonadism, socially embarrassing galactorrhea, or pituitary adenoma
- ✓ Pituitary apoplexy may be suggested by sudden-onset severe central headache with severe malaise, nausea, vomiting, and hypotension with or without visual disturbances
- ✓ Central DI—treatment is with desmopressin to control nocturnal polyuria
- ✓ Central DI—if the thirst mechanism is deranged, close monitoring of the blood pressure and sodium is indicated

ADH Excess: SIADH

Etiologic Factors

ADH excess in the absence of a hyperosmolar stimulus may be appropriate when it occurs in response to hypovolemia or hypotension and inappropriate when it occurs in the absence of a hypovolemic or hypotensive stimulus. SIADH can result from exogenous or endogenous disorders.

Exogenous ADH excess may result from the inappropriate administration of ADH (or its analogues such as desmopressin) or oxytocin. *Endogenous ADH excess* may originate from a eutopic hypothalamic or an ectopic extrahypothalamic source.

Eutopic ADH excess may be a consequence of 1) central nervous system or hypothalamic disorders (eg, traumatic, inflammatory, degenerative, vascular, or neoplastic disorders); 2) the use of agonist drugs that enhance ADH secretion or action (chlorpropamide, carbamazepine, vincristine, vinblastine, cyclophosphamide, phenothiazines, monoamine oxidase inhibitors, tricyclic antidepressants, and clofibrate); or 3) neurogenic influences such as pain or nausea.

Ectopic extrahypothalamic ADH excess may result from 1) malignancies (cancers of the bronchus, pancreas, ureter, prostate, or bladder; lymphoma; leukemia; thymoma; or mesothelioma) or 2) benign pulmonary disorders (pneumonia, lung abscess, empyema or pneumothorax, tuberculosis, cystic fibrosis, and the use of positive-pressure ventilation).

Pathophysiologic Characteristics

Continued water intake and ADH hypersecretion in the absence of a hyperosmolar stimulus lead to increased renal water retention, hyponatremia, and hypo-osmolality of body fluids with inappropriately concentrated urine. Homeostatic adjustments promote renal escape and natriuresis, including increased glomerular filtration rate, increased levels of atrial natriuretic hormones, and suppression of the renin-angiotensin-aldosterone axis. Natriuresis exacerbates plasma hypo-osmolality, thus explaining the absence of edema.

Clinical Features

The clinical features of SIADH are a composite of the effects of the underlying disorder and those of the hyponatremic syndrome that depend on the degree and rapidity of its development. Patients with SIADH may be asymptomatic if the hyponatremia is mild or has developed gradually over weeks and months. When patients are symptomatic, the most frequent symptoms are lethargy, fatigue, ill health, anorexia, nausea and vomiting, headache, and irritability or confusion. Severe or rapidly developing hyponatremia can lead to a behavioral change, a change in the level of consciousness, or seizures.

Diagnosis

An appropriate ADH excess is associated with decreased cardiac output, renal failure, hepatic failure (hypervolemic), and dehydration (hyperosmolar and hypovolemic). SIADH is suspected when a patient has clinical euvolemia and hyponatremia. Hyperosmolar states and loss of intracellular water to the hyperosmolar extracellular fluid should be excluded first, as for hyperglycemic patients or patients who have received mannitol (ie, plasma glucose, history of mannitol use, and increased plasma osmolality). Those patients do not have hypo-osmolality. True hyponatremia should then be confirmed. Now that sodium levels are measured with direct potentiometric ion-selective electrodes, so-called pseudohyponatremia from elevated triglyceride levels (severe) or increased protein (in monoclonal gammopathy) is not seen.

If hyponatremia and reduced serum osmolality have been documented in a patient with clinical euvolemia, thyroid function tests (free T_4 and thyrotropin) and cortisol measurements should be performed. These hormones are important for free water clearance. Hypothyroidism or cortisol deficiency (both from a primary or hypothalamopituitary cause) can cause hyponatremia with hypo-osmolality.

The main diagnostic challenge is to differentiate SIADH from subclinical hypovolemia. Urinary sodium concentration, serum creatinine or uric acid levels, plasma renin activity, and the aldosterone level are measured. In contrast to findings in SIADH, subclinical hypovolemia is associated with a urinary sodium concentration less than 20 mmol/L, increased serum creatinine and uric acid levels, and an increased plasma renin activity and plasma aldosterone level.

Therapy

Therapy for SIADH includes identification and management of the underlying disorder. Restriction of total water intake controls symptomatic hyponatremia (a good starting point is 800-1,000 mL of water daily, including water in food, drinks, and free water). Specific ADH antagonists, the vaptans, have become available (tolvaptan for oral use and conivaptan for intravenous use). These selective or nonselective vasopressin V2-receptor antagonists are indicated currently for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium ≤125 mmol/L with marked hyponatremia that is symptomatic and has resisted correction with fluid restriction). These drugs are used during hospitalization and with close monitoring of clinical status and serum sodium.

When acute neurologic sequelae are present, hypertonic saline can be given intravenously (200-300 mL of 5% saline over 3-4 hours). Serum sodium should be gradually increased (not to exceed 0.5 mmol/hour or 12 mmol in 24 hours). Hypertonic saline should be given until the neurologic symptoms cease and a "safe" serum sodium level of 120 mmol/L is reached. Rapid correction of hyponatremia (eg, >12 mmol/L in 24 hours) can cause osmotic central pontine myelinolysis, which often is fatal.

18 Thyroid Disorders

MARIUS N. STAN, MD

Laboratory Assessment of Thyroid Function

Serum Thyrotropin

Current assays measure thyrotropin (also called *thyroid-stimulating hormone* [TSH]) concentrations as low as 0.01 mIU/L, allowing differentiation between low-normal values and suppressed values. In patients with a normal pituitary gland, thyrotropin levels are increased in primary hypothyroidism, during recovery from nonthyroid illness, and with thyroid hormone resistance. Thyrotropin levels are low in hyperthyroidism, in nonthyroidal illness, in the first trimester of pregnancy, and with the use of certain drugs (eg, somatostatin, dopamine, and glucocorticoids). The assay can be spuriously affected by biotin (used frequently as a supplement), which should be discontinued at least 12 hours before blood collection. Occasionally, thyrotropin heterophile antibodies can be present and affect thyrotropin measurement; a laboratory workup for their presence should be triggered by clinical inconsistencies. Overall, though, measurement of the thyrotropin level is the best single test of thyroid function in these patients.

In patients with pituitary disease, however, thyrotropin levels are unreliable since the values can be inappropriately normal in relation to thyroid hormone concentrations. Thus, thyrotropin levels may be normal or increased in patients with thyrotropin-producing tumors and normal or decreased in patients with central hypothyroidism.

Thyroxine

Free Thyroxine

Although the free thyroxine (T_4) concentration is frequently measured, the accuracy of the assays available for clinical use differs substantially. Serum free T_4 is decreased in hypothyroidism and the late phase of nonthyroidal illness and increased in hyperthyroidism, in the initial phase of nonthyroidal illness, and in thyrotropin-producing pituitary tumors or thyroid hormone resistance. This assay can have spurious results from biotin supplement use.

Total Thyroxine

Measurement of the total T_4 concentration includes T_4 bound to thyroid hormone–binding proteins (99.98% of total T_4), unbound T_4, and free T_4. Therefore, conditions that affect the concentration of binding proteins (mainly thyroxine-binding globulin [TBG]) will affect total T_4 measurements. Androgens, anabolic steroids, glucocorticoids, chronic liver disease, niacin, and familial TBG deficiency decrease total TBG concentrations. Estrogens (including during pregnancy), acute hepatitis, and familial TBG excess increase TBG concentrations and, therefore, total T_4 concentrations.

Total Triiodothyronine

Similar to total T_4, the serum total triiodothyronine (T_3) concentration is decreased in hypothyroidism, in nonthyroidal illness, with the use of drugs that decrease the binding proteins, and with caloric deprivation. It is also decreased with drugs that inhibit the conversion of T_4 to T_3 (eg, propranolol, amiodarone, glucocorticoids). Serum T_3 levels are increased in thyrotoxicosis and thyroid hormone resistance. Serum T_3 concentrations should be measured to establish or exclude the diagnosis of T_3 thyrotoxicosis in a patient who has a low thyrotropin level and a normal T_4 level.

Thyroid tests are always necessary to diagnose subclinical thyroid disease. In subclinical hyperthyroidism, the thyrotropin level is suppressed, but T_3 and T_4 levels are normal. In subclinical hypothyroidism, the thyrotropin level is elevated, but T_3 and T_4 levels are normal (Table 18.1).

Table 18.1 • Interpretation of Thyroid Function Test Results

Serum Concentration			
Thyrotropin	**Free T_4**	**T_3**	**Diagnosis**
Normal	Normal	Normal	Normal
High	Low	Normal or low	Primary hypothyroidism
High	Normal	Normal	Subclinical hypothyroidism
Low	High or normal	High	Hyperthyroidism
Low	Normal	Normal	Subclinical hyperthyroidism

Abbreviations: T_3, triiodothyronine; T_4, thyroxine.

Thyroid Hormone–Binding Proteins

Measurement of thyroid hormone–binding proteins (eg, TBG, transthyretin, albumin) can be helpful when a discrepancy exists between total thyroid hormone concentrations and the results of other thyroid tests. The concentration of these proteins can be altered by medications (as described above), pregnancy, hepatitis, acute intermittent porphyria, terminal illness, hypothyroidism, and hyperthyroidism, or they can be abnormal because of an inherited condition (eg, TBG deficiency, TBG excess). Similarly, their affinity for T_4 and T_3 can be altered by medications (eg, increased with estrogens, decreased with androgens) or affected by inherited conditions.

Thyroid Scanning

Thyroid scanning shows the distribution of functioning thyroid tissue. It distinguishes between hyperthyroidism caused by Graves disease and toxic thyroid nodules and identifies ectopic thyroid tissue and metastatic disease in the follow-up of patients with differentiated thyroid cancer.

Radioactive Iodine Uptake

Results of the radioactive iodine uptake (RAIU) test represent the percentage of radioactive iodine retained for a specific time (usually 24 hours) after it is administered. RAIU is indicated during the evaluation of hyperthyroidism to distinguish between low- and high-uptake states and to aid in dose calculations when radioactive iodine is used to treat Graves disease.

Serum Thyroglobulin

Thyroglobulin is used as a tumor marker in patients who have a differentiated thyroid carcinoma. It is also useful in the differential diagnosis of hyperthyroidism, to distinguish between an endogenous hormone source (increased thyroglobulin) and an exogenous hormone source (suppressed thyroglobulin).

Thyrotropin Receptor Antibodies

Thyrotropin receptor antibodies (TRAbs) are a mixture of stimulating, inhibitory, and neutral antibodies. Some laboratories measure the stimulating fraction of TRAbs, called *thyroid-stimulating immunoglobulins*. TRAbs are markers of autoimmunity and are useful for diagnosing Graves disease in patients who cannot undergo RAIU testing (eg, pregnant women). In women with active Graves disease or a history of it, an elevated TRAb level in the last trimester of pregnancy predicts an increased risk of neonatal hyperthyroidism. The TRAb assay can also be falsely affected by biotin use (often as a supplement), which should be discontinued at least 12 hours before blood collection.

Thyroglobulin and Thyroperoxidase Antibodies

Thyroglobulin and thyroperoxidase antibodies are used as markers of autoimmune thyroid disease. However, their absence does not exclude autoimmune thyroid disease. Conversely, they can be found in healthy persons. High titers occur in more than 90% of patients with Hashimoto thyroiditis. When thyroglobulin antibodies are present, the measurement of thyroglobulin by immunoassay is unreliable for follow-up of thyroid malignancies. The liquid chromatography mass spectroscopy assay is able to circumvent this problem.

Thyroid Ultrasonography

Ultrasonography is used for the anatomical assessment of thyroid nodules and goiter, for assessment of thyroid vascularity, and for the follow-up of patients after thyroid cancer treatment.

KEY FACTS

- ✓ In pituitary disease, thyrotropin levels are unreliable (may appear normal in relation to thyroid hormone levels)
- ✓ Discrepancies between total thyroid hormone levels and other thyroid function tests may be resolved by measuring thyroid hormone–binding protein levels
- ✓ Thyroid scanning—distinguishes between Graves disease and toxic thyroid nodules as the cause of hyperthyroidism; also identifies ectopic thyroid tissue and metastatic disease in follow-up
- ✓ Thyroglobulin—tumor marker for differentiated thyroid carcinoma; also distinguishes between endogenous and exogenous hormone sources

Hyperthyroidism

Etiologic Factors

The primary thyroid disorders that cause hyperthyroidism can be divided into those characterized by increased production and release of T_4 (high RAIU) and those characterized by unregulated release of T_4 because of gland destruction (low RAIU) (Box 18.1). From the nonthyroidal causes of increased thyroid hormone levels, exogenous hyperthyroidism is the most common one. It is noted particularly in patients receiving combination T_4 and T_3 treatment. (Of note, thyroid hormones also have been detected in some supplements not explicitly described to contain thyroid hormones.) Other nonthyroidal causes to consider are struma ovarii and large metastatic deposits of follicular carcinoma, which can lead to excess thyroid hormone production. These nonthyroidal causes are associated with low RAIU over the thyroid area.

Graves disease is the most common thyroid-related cause of hyperthyroidism in the United States. Other common causes are toxic nodular goiter and thyroiditis (lymphocytic or subacute).

Clinical Features

Most clinical features of hyperthyroidism reflect the effects of excess thyroid hormone. Typical symptoms and signs are listed in Box 18.2. Most patients with hyperthyroidism have a small (1 to 2 times the normal size), firm goiter.

Graves orbitopathy is specific for hyperthyroidism caused by Graves disease. Ocular manifestations include findings due to sympathetic overactivity from hyperthyroidism of any cause (retraction of the upper lid, stare, and lid lag), along with findings unique to Graves orbitopathy (lid edema, conjunctival injection, chemosis, proptosis, and extraocular muscle weakness). Patients with Graves orbitopathy may report a gritty sensation in the eyes, excessive lacrimation, photophobia, and diplopia. Graves dermopathy also can develop in these patients, manifesting as an indurated, erythematous, thickened skin area, usually over the shins.

Box 18.1 • Etiologic Factors of Hyperthyroidism According to Radioactive Iodine Uptake (RAIU)

- Normal or increased RAIU over the neck
  - Graves disease
  - Toxic nodule or toxic multinodular goiter
  - Thyrotropin-producing pituitary adenoma
  - Thyroid hormone resistance (clinically euthyroid usually)
  - Trophoblastic disease
- Low or nearly absent RAIU over the neck
  - Painless lymphocytic thyroiditis
  - Subacute painful thyroiditis
  - Amiodarone-induced thyroiditis
  - Iatrogenic thyrotoxicosis
  - Struma ovarii

Box 18.2 • Common Symptoms and Signs of Hyperthyroidism

- Symptoms
  - Heat intolerance
  - Palpitations
  - Nervousness
  - Irritability
  - Insomnia
- Signs
  - Tachycardia
  - Increased sweating
  - Diarrhea
  - Weight loss
  - Muscle weakness (proximal)

Elderly patients with hyperthyroidism may present with atypical findings that include apathy, weight loss, supraventricular tachyarrhythmia, and congestive heart failure. This presentation is called *apathetic thyrotoxicosis*. Separately, gynecomastia may develop in younger men.

Diagnosis

The diagnosis of hyperthyroidism is biochemical: low serum thyrotropin level combined with an elevated level of T_3 or T_4, or both. A low serum thyrotropin level alone with normal T_3 and T_4 concentrations is consistent with subclinical hyperthyroidism, but it has to be in the right clinical context. It is important to remember that an isolated low thyrotropin level can also be encountered in nonthyroid illness, glucocorticoid therapy, dopamine therapy, and secondary hypothyroidism.

Specific Causes

Graves Disease

Graves disease is characterized by hyperthyroidism with diffuse RAIU and the presence of TRAbs, which have a stimulatory effect on the thyrotropin receptor, causing the hyperthyroidism. The disease is more common in young women and causes the thyroid to be mildly enlarged and firm.

Graves orbitopathy and pretibial dermopathy are usually associated with Graves disease. TRAbs are the pathophysiologic link between them. Treating hyperthyroidism is an important first step in the management of these conditions. Both conditions tend to improve in response to hyperthyroidism treatment when it is initiated early in the disease process.

Painless Thyroiditis

Painless thyroiditis (also called *postpartum thyroiditis* or *silent thyroiditis*) is usually a self-limiting disease that occurs most commonly in the postpartum period and tends to recur with subsequent pregnancies. However, it also can occur unrelated to pregnancy and in men.

The classic presentation is a sequential triphasic pattern: 1) the hyperthyroid phase, with suppressed thyrotropin, low RAIU, and increased levels of free T_3 and T_4; 2) the hypothyroid phase; 3) the recovery phase, with normal thyroid function. This triphasic pattern may be abbreviated such that all 3 phases are not apparent in all patients.

Treatment is symptomatic. β-Blockers may be needed during the hyperthyroid phase, and temporary thyroid hormone replacement may be necessary during the hypothyroid phase. In some cases, the hypothyroidism may be permanent.

Antithyroid medication or radioactive iodine therapy is not indicated because the hyperthyroidism results from the release of preformed thyroid hormone, not from increased production.

Subacute Granulomatous Thyroiditis

Subacute granulomatous thyroiditis (also called *de Quervain thyroiditis*) is characterized by a painful tender goiter. Patients often report fever, malaise, myalgia, and a history of upper respiratory tract infection. Transient hyperthyroidism (low RAIU) is often present at diagnosis and may be followed by transient hypothyroidism. The erythrocyte sedimentation rate is invariably increased.

Treatment is symptomatic. β-Blockers and thyroid hormone replacement are used as discussed for painless thyroiditis. Nonsteroidal anti-inflammatory drugs and corticosteroids are useful for pain in thyroiditis. The response to corticosteroid therapy is dramatic, typically with relief of symptoms within 24 hours. This type of thyroiditis is unlikely to recur.

Multinodular Goiter

Toxic multinodular goiter occurs in patients with a longstanding nodular goiter, in which autonomous functioning nodules develop. The hyperthyroidism is usually mild, yet cardiovascular manifestations tend to dominate. The goiter is large, nodular, and asymmetrical. In patients with retrosternal extension or a short neck, the thyroid may be difficult to palpate. Patients are at risk for exacerbation of symptoms from iodine-induced hyperthyroidism due to exposure to iodinated contrast media.

Toxic Thyroid Adenoma

Toxic thyroid nodules are follicular adenomas with autonomously increased thyroid hormone production. The nodule is solitary (usually >3 cm) and found in middle-aged women. It is easy to palpate and has a firm consistency. A radioisotope scan shows intense uptake in the nodule, with suppressed uptake in the rest of the gland.

Exogenous Hyperthyroidism

Exogenous hyperthyroidism can result from the use of T_4 or T_3 supplementation (or both). It should be suspected when patients with thyrotoxicity have low RAIU and no palpable goiter. Low serum levels of thyroglobulin help to differentiate this disorder from painless thyroiditis.

Therapy

Thionamides

Methimazole and propylthiouracil (PTU) are the main thionamides and can be used to treat hyperthyroidism due to increased production of thyroid hormone. They act by blocking thyroid hormone synthesis. Thionamides are used in Graves disease to control hyperthyroidism, with the hope that the disease will undergo spontaneous remission during therapy. Treatment is typically given for 12 to 18 months and then discontinued. The effect of thionamides is temporary, and hyperthyroidism often recurs after discontinuation. In about 50% of patients, the disease relapses within the first 12 months after treatment is stopped. However, an evolving approach is to use thionamides for long-term treatment as long as they are well tolerated and the patient does not want to completely eliminate the thyroid.

Potentially serious adverse effects include agranulocytosis and hepatitis. Agranulocytosis can develop abruptly, and its development seems to be dose related. Patients with agranulocytosis typically have fever and oropharyngeal infections (sore throat). Hepatitis is more common with PTU; therefore, methimazole is the drug of choice. The exceptions favoring the use of PTU instead of methimazole are thyroid storm (PTU decreases T_3 levels faster because it inhibits the conversion of T_4 to T_3) and the first trimester of pregnancy (PTU is less teratogenic than methimazole).

Radioactive Iodine

Radioactive iodine therapy effectively ablates the thyroid gland. For high-RAIU hyperthyroidism, radioactive iodine has been the most commonly used therapy in the United States. It now gradually is being overtaken by thionamides. The goal of therapy is to render the patient hypothyroid, and the maximal effect is apparent within 2 to 3 months. Treatment of toxic multinodular goiter requires higher doses of radioactive iodine and often more than 1 course of treatment. Radioactive iodine therapy has not been associated with long-term risks, but pregnancy and breastfeeding are contraindications. Although radioactive iodine therapy can worsen the course of active Graves orbitopathy, that worsening can be avoided with the prophylactic use of glucocorticoids.

Surgical Procedures

Near-total or total thyroidectomy is used infrequently for the treatment of Graves disease or toxic multinodular goiter. If nodules appear suspicious with fine-needle aspiration (FNA), surgery should be strongly considered. Thyroid lobectomy is used for toxic thyroid adenoma. In addition, surgery is usually considered when *rapid* restoration of a euthyroid state is desired, such as when the patient is pregnant and large doses of thionamides are needed to control hyperthyroidism or the patient has a large compressive goiter. Damage to the recurrent laryngeal nerves or parathyroid glands is uncommon (<1%-2%) with experienced surgeons. To prevent thyroid storm and excessive bleeding from the overactive friable gland, the patient should be treated preoperatively with stable iodine solution in combination with antithyroid drug therapy and β-blockers. This approach should render the patient euthyroid or nearly euthyroid at the time of operation.

Supportive Therapy

Symptomatic patients should be given β-blockers to control adrenergic manifestations of hyperthyroidism while they wait for definitive therapy to take effect.

Thyroid Storm

Thyroid storm is a state of life-threatening hyperthyroidism with severe multisystem manifestations. It develops in patients who have acute illness superimposed on uncontrolled thyrotoxicosis and patients who have a sudden increase in thyroid hormone levels from intraoperative thyroid manipulation or radiation-induced thyroiditis. Thyroid storm is usually characterized by delirium, fever, tachycardia, hypotension, vomiting, diarrhea, and, eventually, coma. Treatment should be initiated immediately in the intensive care unit. Antithyroid therapy with PTU is preferred. Iodine solution is added to inhibit the release of preformed thyroid hormone and to decrease peripheral conversion of T_4 to T_3. β-Blocker therapy, corticosteroid therapy, supportive therapy directed at systemic disturbances, and therapy directed at the precipitating event should be delivered in parallel.

KEY FACTS

- ✓ Primary thyroid disorders causing hyperthyroidism—high RAIU (increased T_4 production and release) or low RAIU (unregulated T_4 release from gland destruction)
- ✓ Graves disease—hyperthyroidism with diffuse RAIU; TRAbs stimulate thyrotropin receptors
- ✓ Thyroid storm—acute illness and uncontrolled thyrotoxicosis or suddenly increased thyroid hormone levels (from intraoperative thyroid manipulation or radiation-induced thyroiditis)

Key Definition

Thyroid storm: ***life-threatening hyperthyroidism with severe multisystem manifestations.***

Hypothyroidism

Hypothyroidism can be primary (intrinsic thyroid disease) or secondary (hypothalamic-pituitary disease). Primary hypothyroidism accounts for more than 99% of all cases.

Etiologic Factors

The most common cause of hypothyroidism in the United States is Hashimoto thyroiditis, an autoimmune thyroid disease. It tends to cluster in families and is more common in women. Other causes of hypothyroidism include radioactive iodine treatment of hyperthyroidism, thyroidectomy, and radiotherapy for neck malignancies. Transient hypothyroidism may occur during the course of subacute granulomatous thyroiditis or painless thyroiditis. Hypothyroidism can also occur after drug-induced thyroiditis related to tyrosine kinase inhibitors, angiogenesis inhibitors (eg, lenalidomide), or immune checkpoint inhibitors (eg, ipilimumab, pembrolizumab).

Clinical Features

The clinical manifestation of hypothyroidism depends on the degree and duration of the deficiency. When symptoms are present, they are nonspecific (Box 18.3). Many patients are asymptomatic at presentation, with hypothyroidism having been diagnosed through routine screening.

Macrocytic anemia (due to pernicious anemia or autoimmune disease) or microcytic anemia (iron deficiency due to menorrhagia) may be present in hypothyroidism. Patients with prolonged increases in thyrotropin may have galactorrhea (thyrotropin-releasing hormone stimulates prolactin secretion). Rarely, patients may have psychosis, deafness, or cerebellar

Box 18.3 • Common Symptoms and Signs of Hypothyroidism

Symptoms
  Fatigue
  Cold intolerance
  Muscle cramps
  Mental slowing
  Constipation
Signs
  Coarse skin
  Dry hair
  Weight gain
  Periorbital puffiness
  Delayed ankle reflex

ataxia (or any combination of these). Patients who have respiratory depression may also have central hypoventilation and apnea. Hyponatremia due to a syndrome of inappropriate secretion of antidiuretic hormone may be present. Associated laboratory findings include hyperlipidemia and increased levels of aspartate aminotransferase, lactate dehydrogenase, or creatine kinase. When hypothyroidism is identified, another consideration is the possibility of associated endocrinopathies as part of a polyglandular autoimmune syndrome (Addison disease, type 1 diabetes mellitus, hypoparathyroidism, hypogonadism, or pernicious anemia). Hypothyroidism may also be associated with vitiligo and other autoimmune or connective tissue diseases.

Diagnosis

If nonthyroidal illness has been excluded, low T_4 and increased thyrotropin levels are diagnostic of overt primary hypothyroidism. Subclinical hypothyroidism is identified when the thyrotropin level is elevated but the T_4 level is normal. Hashimoto thyroiditis is usually associated with a firm goiter and a high titer of antimicrosomal (thyroid peroxidase) antibodies. A low T_4 level and an inappropriately normal or low thyrotropin level indicate secondary hypothyroidism. If this is in the clinical setting of acute illness, the patient might have transient central hypothyroidism (previously known as *sick euthyroid syndrome*), and no further investigation is required. Otherwise, magnetic resonance imaging of the head should be performed in addition to pituitary function tests.

Therapy

For overt hypothyroidism, thyroid hormone replacement therapy is initiated with synthetic T_4 (levothyroxine). The goals of therapy are to normalize thyrotropin values in primary hypothyroidism and to normalize T_4 values in secondary hypothyroidism. Failure to normalize thyrotropin concentrations may indicate poor adherence to drug therapy, decreased absorption due to concomitant use of interfering medications (eg, sucralfate, calcium supplements, or ferrous sulfate), or gastrointestinal tract disease. Other possibilities include progressive thyroid disease, increased thyroid-binding proteins (as with pregnancy or estrogen use), and increased hormone clearance (eg, with phenytoin, carbamazepine, or tyrosine-kinase inhibitors). Thyrotropin levels should be assessed annually or as indicated by the patient's symptoms.

Miscellaneous Circumstances

T_4 Replacement Therapy in Pregnancy

Most women with primary hypothyroidism require an increase in the levothyroxine dose during pregnancy (average increase, 25%-30%). Women receiving T_4 replacement therapy should be counseled about the importance of ensuring adequate replacement *before* conception because of the importance of maternal thyroid hormone in fetal organogenesis and because of the multiple potential complications related to hypothyroidism for both mother and fetus, including first-trimester spontaneous abortion, preterm delivery, and perinatal morbidity and death. Thyrotropin levels should be assessed periodically during pregnancy and the T_4 dose adjusted as necessary to maintain a normal thyrotropin for the specific trimester of pregnancy.

T_4 Replacement Therapy for Patients With Cardiac Disease and for Elderly Patients

Replacement T_4 therapy for elderly patients and patients who have coronary artery disease should start at a low dose (25-50 mcg daily) and increase gradually until the thyrotropin level is normal. Hypothyroidism is not a contraindication for cardiac intervention, although the patient would have an increased risk of hyponatremia and other perioperative complications.

Subclinical Hypothyroidism

Subclinical hypothyroidism is a relatively common disorder that affects 5% to 15% of elderly patients. The risk of progression to overt hypothyroidism increases with age, the presence of thyroid antibodies, and thyrotropin levels greater than 10 mIU/L. The actual decision to treat subclinical hypothyroidism depends on the degree of thyrotropin elevation. There is a clear consensus to treat when thyrotropin values are greater than 10 mIU/L. However, uncertainty exists about the benefit of therapy when thyrotropin is between upper end of normal and 10 mIU/L. In the latter group, a trial of replacement therapy is indicated for symptomatic patients and for patients at risk for progressive disease.

Myxedema Coma

Myxedema coma is severe life-threatening hypothyroidism. It occurs in patients who have severe untreated hypothyroidism with a superimposed acute illness (eg, infection, surgical procedure, or myocardial infarction), have exposure to cold, or use sedatives or opiates. The onset is insidious, with progressive stupor culminating in coma. Seizures, hypothermia, hypotension, hypoventilation, hyponatremia, and hypoglycemia may be present. The mortality rate is high (20%-30%). Treatment should be initiated promptly in an intensive care unit with intravenous T_4 with or without T_3 and with supportive measures.

Key Definition

Myxedema coma: *life-threatening, untreated, severe hypothyroidism with superimposed acute illness, exposure to cold, or use of sedatives or opiates.*

Thyroid Nodules

Thyroid nodules are common, and their frequency increases with age. They may be noticed by the patient, detected during a routine medical examination, or detected during neck imaging performed for other reasons. When nodules are identified, the primary concern is whether they are benign or malignant. At least 95% of palpable thyroid nodules are benign. The likelihood of malignancy increases with a family history of thyroid carcinoma, hoarseness, the presence of cervical adenopathy, and a history of radiotherapy to the head and neck (especially during childhood).

Evaluation should begin with a thyrotropin measurement to determine whether the nodule functions autonomously. Malignancy is substantially less likely if the thyrotropin level is suppressed, in which case a radioactive iodine scan and an RAIU test should be performed. A nontoxic nodule should be sampled by ultrasound-guided FNA if it is larger than 1 to 2 cm (depending on clinical and ultrasonographic risk factors for malignancy). Thyroid FNA has high sensitivity and specificity for excluding malignancy when the FNA is performed and interpreted by experienced physicians. If the aspirate is benign, annual follow-up with palpation, thyroid ultrasonography, and thyrotropin measurement are adequate. A change in nodule size requires consideration of another biopsy. A nondiagnostic aspirate requires additional aspiration in this case. If the aspirate is interpreted as suspicious or compatible with malignancy, surgical intervention is required. Compressive symptoms (dysphonia, dysphagia, and dyspnea) should prompt surgical intervention even if the nodule is benign.

Thyroid Cancer

Differentiated Thyroid Cancers

Papillary Thyroid Carcinoma

Papillary thyroid carcinoma is the most common type of thyroid cancer (80%-90% of cases). It has a bimodal incidence distribution, with increased incidence in early adulthood and again in late adulthood. Dissemination is typically lymphatic. Lung and bone metastases may occur. Usually found as a thyroid nodule, papillary thyroid carcinoma may also manifest as cervical adenopathy or as an incidental finding in an excised thyroid gland.

Follicular Carcinoma

Follicular carcinoma is the diagnosis in 10% to 15% of thyroid cancer cases. It typically spreads hematogenously. The usual manifestation is a thyroid mass or metastases to the lungs, bones, or brain. Rarely, it causes thyrotoxicosis if the tumor burden is large.

Other Thyroid Cancers

Anaplastic Carcinoma

Anaplastic carcinoma typically manifests as a rapidly enlarging thyroid mass that causes pain and compressive local neck symptoms. It is highly undifferentiated, and the prognosis is poor (1-year survival is about 50%).

Medullary Thyroid Carcinoma

Medullary thyroid carcinoma is a neuroendocrine tumor that produces calcitonin. It is part of a familial syndrome in 25% of cases (multiple endocrine neoplasia type 2 [MEN2]). It typically manifests as a solitary nodule or a dominant nodule in a multinodular goiter, and it is frequently metastatic at diagnosis, with 50% of patients having lymph node involvement. Tumor production of hormonal substances can lead to diarrhea and facial flushing or Cushing syndrome. Because there are *RET* proto-oncogene mutations are present in the familial form, patients with medullary thyroid carcinoma should be offered genetic testing. If a familial form is identified, the patients should also be screened for the additional components of MEN2: pheochromocytoma and primary hyperparathyroidism. Median survival for medullary thyroid carcinoma is less than for differentiated thyroid malignancies but considerably better than for anaplastic carcinoma.

Management of Thyroid Malignancy

Surgical excision is the therapy of choice for differentiated thyroid cancer and medullary thyroid carcinoma. Excision of anaplastic carcinoma may be undertaken as part of multimodality therapy or to palliate tracheal compression. Papillary cancer carries the best prognosis of all thyroid cancers. Factors associated with a poorer prognosis include age older than 55 years at diagnosis, incomplete resection, extensive local invasion, large primary tumor, and presence of distant metastases. Cervical lymph node involvement does not affect the prognosis.

Patients at high risk for recurrence often undergo radioactive iodine therapy to ablate the thyroid remnant. Suppressive levothyroxine therapy is also pursued for these patients, with the target thyrotropin level of less than 0.1 mIU/L. Patients at low risk for recurrence do not require thyroid remnant ablation and are treated with thyroid hormone replacement to maintain thyrotropin in the lower half of the reference range (0.1-2.5 mIU/L). Patients should be reevaluated 3 to 6 months later and annually thereafter. Most differentiated thyroid cancers synthesize and secrete thyroglobulin, which can be used as a marker of recurrent or persistent disease. Whole-body iodine scanning and neck ultrasonography are also used widely to monitor patients after treatment of thyroid cancer. Recurrences are usually treated with excision or radioactive iodine, depending on location.

Miscellaneous Thyroid Disorders

Transient Central Hypothyroidism (Previously Known as Sick Euthyroid Syndrome)

Patients with systemic illness frequently have abnormal thyroid function test results without identifiable intrinsic thyroid disease. The abnormalities are suggestive of central hypothyroidism but resolve with recovery from the acute illness. Thyroid hormone therapy is not indicated because it has not been proven to improve the prognosis for these patients. The main challenge is to distinguish between nonthyroid illness and intrinsic thyroid or pituitary disease because the thyrotropin level may be normal or low initially but increase during recovery. Thyroid testing of inpatients should be avoided in the absence of specific features suggestive of thyroid disease (eg, goiter, extrathyroidal manifestations of Graves disease, hypopituitarism, arrhythmias).

KEY FACTS

✓ Primary hypothyroidism therapy in pregnancy—women usually need to increase levothyroxine dose by 25% to 30%

✓ Palpable thyroid nodules—most (≥95%) are benign; increased malignancy risk with solitary nodules, older age, male sex, and head and neck radiotherapy (especially in childhood)

✓ Papillary thyroid carcinoma—most common thyroid cancer (80%-90%); bimodal distribution (younger adults and older adults)

✓ Transient central hypothyroidism (formerly called *sick euthyroid syndrome*)—avoid thyroid testing of inpatients who do not have characteristics of thyroid disease (eg, goiter, Graves disease, hypopituitarism, arrhythmias)

Amiodarone and Thyroid Dysfunction

With its high iodine content, amiodarone causes thyroid dysfunction in about 15% of patients who receive it. Amiodarone-associated thyroid dysfunction is more likely in patients with preexistent thyroid abnormalities. The most common abnormality in iodine-replete geographic areas is hypothyroidism. Hyperthyroidism may be caused by an increase in thyroid hormone production (type 1) or a destructive thyroiditis (type 2). Medical therapy is less effective than for other causes of hyperthyroidism; in some cases, thyroidectomy is needed. Periodic monitoring of thyroid function is essential for patients treated with amiodarone, particularly elderly patients.

III Questions and Answers

Questions

Multiple Choice (Choose the best answer)

III.1. A 52-year-old man had blood work performed as part of a routine physical examination for work. The serum calcium value was noted to be 10.8 mg/dL (reference range, 8.9-10.1 mg/dL). A repeat value performed 1 month later was also modestly elevated, at 10.7 mg/dL. The patient does not recall having a serum calcium value checked previously. Additional laboratory tests associated with the serum calcium value of 10.7 mg/dL included a parathyroid hormone (PTH) level of 72 pg/mL (reference range, 15-65 pg/mL), 25-hydroxyvitamin D level of 38 ng/mL (reference range, 25-50 ng/mL), and creatinine concentration of 0.9 mg/dL (reference range, 0.8-1.3 mg/dL). The patient is the sole child of his parents. He is unsure whether either of his parents had hypercalcemia, and both are now deceased. Clinically, he feels well. He has never had nephrolithiasis. Physical examination is normal. What is the next best step in management?

a. Parathyroid sestamibi imaging
b. Bone mineral density (dual energy x-ray absorptiometry [DXA]) testing
c. Ultrasonography for parathyroid gland localization
d. Twenty-four–hour urine collection for calcium and creatinine

III.2. Therapy for a 68-year-old woman was started with alendronate 70 mg once weekly 3 years ago for osteoporosis identified on routine bone mineral density (dual energy x-ray absorptiometry [DXA]) imaging. Her diet provides approximately 1,200 mg of calcium daily, and she also takes a daily tablet of 1,000 international units of vitamin D_3 (cholecalciferol). A DXA scan performed last week (3 years from her previous study) shows statistically significant declines at the lumbar spine (–5.6%), total hip (–4.1%), and femoral neck (–4.4%). The patient has continued to be physically active with a program of walking for 30 to 60 minutes daily, and states that overall she feels well. Laboratory studies show normal values for serum calcium, creatinine, 25-hydroxyvitamin D, parathyroid hormone, and 24-hour urine calcium. Physical examination is normal and unchanged from 3 years ago. What is the most likely reason for the noted declines in bone mineral density?

a. Nonresponse to alendronate treatment
b. Unrecognized malabsorption
c. Nonadherence to alendronate treatment
d. Technical error related to positioning by DXA technician

III.3. A 56-year-old healthy man tripped while jogging and landed on his right knee. Due to lingering pain over the patella, he presented 2 weeks later to his primary care provider, who ordered imaging of his right lower extremity. Although no abnormalities of the patella were noted, an incidental finding of Paget disease of bone was noted in the proximal right femur. An alkaline phosphatase level is 230 U/L (reference range, 45-115 U/L). His primary provider recommends treatment with zoledronic acid, but the patient is reluctant because he overall feels well and has no pain in his right hip.

Which of the following is not an indication for treatment?

a. Involvement near a joint
b. Serum alkaline phosphatase level greater than 1.5 times the upper normal limit
c. Involvement of a weight-bearing bone
d. Involvement of the skull

III.4. A 28-year-old woman has a fasting plasma glucose of 116 mg/dL with hemoglobin A_{1c} (HbA_{1c}) of 6.8%. About 8 years ago, she was told that she has polycystic ovary syndrome and insulin resistance. During her pregnancy 3 years earlier, she had gestational diabetes mellitus that resolved completely after delivery. Since then, the patient has gained about 4 kg, and her current body mass index is 36.6 kg/m^2. Examination shows acanthosis nigricans and stretch marks on her lower abdomen, upper thigh, and upper arms. What is the next best step in the management of this patient?

a. Repeat fasting plasma glucose
b. Repeat HbA_{1c}
c. 75-g oral glucose tolerance test
d. Fasting plasma glucose and insulin

III.5. A 64-year-old man was referred for a review of diabetes mellitus management. He received the diagnosis of diabetes about 20 years ago after routine screening during a follow-up of hypertension. Initially he was treated with metformin, and glyburide was added 3 to 4 years later. About 1 year ago, he started taking saxagliptin, a dipeptidyl-peptidase-4 (DPP4) inhibitor. Over the past few months, he has had shortness of breath and chest discomfort while walking uphill. The patient also reports waking up and sitting by the side of the bed at night with shortness of breath. About 3 weeks earlier, he underwent cardiac catheterization and drug-eluting stent placement in his left main coronary artery. His serum creatinine before the procedure was 1.7 mg/dL. Metformin was discontinued before the procedure by his cardiologist. His current medications are lisinopril 40 mg orally; atorvastatin 40 mg orally; spironolactone 50 mg orally; clopidogrel 75 mg orally; glyburide 10 mg orally; saxagliptin 5 mg orally; multiple vitamin supplement orally; and vitamin D 1,000 U orally. His self-monitored fasting glucose in the morning ranges from 80 to 120 mg/dL. Examination shows a body mass index of 33.8 kg/m^2, bilateral pitting edema, elevated jugular venous pressure, and throat congestion. The patient's laboratory test results 1 week earlier (about 2 weeks after the cardiac catheterization) were hemoglobin, 14.2 g/dL (reference range, 13.5-17.5 g/dL); mean corpuscular volume, 96.4 fL (reference range, 81.2-95.1 fL); red blood cell distribution width, 16.5% (reference range, 11.8%-15.6%); serum vitamin B$_{12}$, 194 ng/L (reference range, 180-914 ng/L); serum methyl malonic acid, 1.2 nmol/mL (reference range, ≤0.40 nmol/mL); fasting plasma glucose, 76 mg/dL (reference range, 70-100 mg/dL); hemoglobin A$_{1c}$, 6.1% (reference range, 4.8%-5.7%); serum creatinine, 1.7 mg/dL (reference range, 0.8-1.3 mg/dL); estimated glomerular filtration rate (eGFR), 42 mL/min/1.73 m^2 (reference range, >60 mL/min/1.73 m^2); serum sodium, 130 mmol/L (reference range, 135-145 mmol/L); serum potassium, 5.8 mmol/L (reference range, 3.6-5.2 mmol/L); serum aspartate aminotransferase, 92 U/L (reference range, 8-48 U/L); and serum alanine aminotransferase, 62 U/L (reference range, 7-55 U/L). In addition to starting vitamin B$_{12}$ supplement treatment, what are the next best steps in the management of this patient's diabetes?

a. Restart metformin and continue glyburide and saxagliptin therapy.
b. Do not restart metformin but continue glyburide and saxagliptin therapy.
c. Restart metformin and discontinue glyburide and saxagliptin, starting liraglutide therapy instead.
d. Do not restart metformin and discontinue glyburide and saxagliptin, starting glipizide extended release and pioglitazone therapy.

III.6. A 25-year-old African American man who has been losing weight for the past 3 weeks presents with a 5-day history of nausea and vomiting. On direct questioning, he reports polyuria and polydipsia in the past 2 weeks. He rarely drinks water; instead, he drinks about two 2-L bottles of cola per day to quench his thirst. His vital signs are the following: afebrile; pulse, 112 beats per minute; blood pressure, 96/70 mm Hg (supine); and respiratory rate, 20 breaths per minute. Physical examination reveals a drowsy obese man (body mass index, 42 kg/m^2) with prominent acanthosis nigricans. Oral mucosa is dry, and his breath has a sweet fruity odor. The rest of the examination is normal. Laboratory tests show metabolic acidosis, elevated ketone level, and hyperglycemia. Arterial pH is 7.0 (reference range, 7.35-7.45); anion gap, 24 mmol/L (reference range, 6-12 mmol/L); serum bicarbonate, 6 mmol/L (reference range, 22-29 mmol/L); β-hydroxybutyrate, 5.2 mmol/L (reference range, <0.4 mmol/L); random plasma glucose, 365 mg/dL (reference range, <160 mg/dL); white blood cell count, 20.5×10^9/L (reference range, 3.5-10.5×10^9/L). The patient's urinalysis shows ketonuria but is otherwise negative. His hemoglobin A$_{1c}$ is 12.7%, and his serum levels are creatinine, 1.1 mg/dL (reference range, 0.8-1.3 mg/dL); sodium, 129 mmol/L (reference range, 135-145 mmol/L); potassium, 5.0 mmol/L (reference range, 3.6-5.2 mmol/L); total calcium, 8.6 mg/dL (reference range, 8.9-10.1 mg/dL); and phosphorus (inorganic), 1.9 mg/dL (reference range, 2.5-4.5 mg/dL). The patient is admitted to the intensive care unit with the diagnosis of severe diabetic ketoacidosis (DKA). His treatment is started with intravenous (IV) 0.9% (normal) saline at a rate of 1 L over the first hour. His treatment order also is for IV regular insulin, given in a 10-U bolus and then at an infusion rate of 10 U per hour. What is the next best step in management of this patient?

a. IV potassium, phosphorus, and bicarbonate
b. IV phosphorus
c. IV bicarbonate
d. IV potassium

III.7. A 40-year-old woman with a history of inflammatory bowel disease presents with features of Cushing syndrome (dehiscent stretch marks, central obesity, proximal muscle weakness), amenorrhea, uncontrolled diabetes mellitus, and hypertension. On direct questioning and review of her medicines, it appears that she is not taking any systemic glucocorticoids and has not received any corticosteroid injections. She is taking the enteric corticosteroid budesonide. Examination shows characteristics of Cushing syndrome with no characteristics of androgen excess. Laboratory test results show the following: electrolytes, normal; fasting plasma glucose, 242 mg/dL; hemoglobin A$_{1c}$, 12.1%; 8:00 AM plasma cortisol, undetectable; corticotropin (ACTH), 8 pg/mL; testosterone, 22 ng/dL (reference range for women age ≥19 years: 8-60 ng/dL). What is the next step in management?

a. Screen for synthetic glucocorticoids.
b. Overnight dexamethasone suppression test
c. ACTH stimulation test
d. Dehydroepiandrosterone-sulfate

III.8. A 32-year-old man who was evaluated yesterday afternoon for reports of "low T" presents to the clinic. On direct questioning, he reports decreased energy level, weight gain, loss of muscle mass, and depression. He has obstructive sleep apnea, for which he uses continuous positive airway pressure regularly. He also reports diminished libido. Examination shows an obese man with a body mass index of 36.2 kg/m^2, fatty breasts with absence of glandular tissue, and normal genitalia. A blood testosterone level from yesterday is 224 ng/dL (reference level for men ≥19 years, 240-950 ng/dL). What is the next step in management?

a. Start therapy of testosterone gel 5 mg daily or intramuscular testosterone 100 mg every 2 weeks.
b. Check of serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin
c. Recheck of testosterone in the morning
d. Referral of patient for obesity consultation

III.9. A 32-year-old woman presents to the emergency department with extreme weakness, nausea, weight loss, and depression 1 month after the birth of her second child. Childbirth was complicated by excessive bleeding after the delivery, retention of placenta, and a need for surgical intervention and transfusion of 6 units of blood. She had milk production for the first day or two, but it stopped thereafter. Evaluation of her inability to lactate revealed the following test results: prolactin, 4.9 ng/mL (reference range, 4.8-23.3 ng/mL); thyrotropin (TSH), 0.1 mIU/L (reference range, 0.3-4.2 mIU/L); serum sodium, 130 mmol/L (reference range, 135-145 mmol/L); serum potassium, 4.2 mmol/L (reference range, 3.6-5.2 mmol/L); and random plasma glucose, 72 mg/dL (reference range, <160 mg/dL). Examination shows a sickly woman reporting nausea. Blood pressure is 110/70 mm Hg with a pulse of 84 beats per minute. What is the next step in management?

a. Radioactive iodine uptake, thyrotropin receptor antibodies, and administration of propranolol for symptom control
b. Check free thyroxine (T_4). If low, start therapy with levothyroxine 75 mcg daily.
c. Start treatment with intravenous saline and hydrocortisone (100 mg followed by 50 mg every 6 hours) after drawing blood for cortisol and free T_4 tests.
d. Start therapy with intravenous saline, hydrocortisone (100 mg followed by 50 mg every 6 hours), and fludrocortisone (0.1 mg daily) after drawing blood for cortisol and free T_4 tests and for corticotropin (ACTH) (cosyntropin) stimulation test.

III.10. A 52-year-old woman has screening blood work results that show an increased hemoglobin A_{1c} of 7.5%. Her lipid components are total cholesterol, 240 mg/dL; high-density lipoprotein cholesterol (HDL-C), 32 mg/dL; low-density lipoprotein cholesterol (LDL-C), 144 mg/dL; and triglycerides, 320 mg/dL. The patient's past history is significant for hypertension, which has been well managed with an angiotensin-converting enzyme inhibitor. Her 10-year risk of cardiovascular disease (CVD) is 8.7%. In addition to a recommendation for lifestyle interventions, what is the next best step in management of her lipids?
a. Fibric acid
b. Niacin
c. Statin
d. Ezetimibe

III.11. A 67-year-old man presents to the emergency department with an ischemic stroke. His past medical history is clinically significant for hypertension (treated with hydrochlorothiazide). He does not have diabetes mellitus. His lipids tests show total cholesterol, 229 mg/dL; high-density lipoprotein cholesterol (HDL-C), 40 mg/dL; and low-density lipoprotein cholesterol (LDL-C), 166 mg/dL. What is the best management strategy for his dyslipidemia?
a. Red yeast rice
b. Moderate-intensity statin
c. High-intensity statin
d. Niacin

III.12. A 55-year-old woman presents to the emergency department with recurrent nausea and vomiting. Her past medical history is clinically significant for depression, nicotine dependence, obesity complicated by type 2 diabetes mellitus, hyperlipidemia, and obstructive sleep apnea. She underwent Roux-en-Y gastric bypass 3 months ago. On examination, she is noted to have horizontal nystagmus elicited with lateral gaze bilaterally. Reflexes are brisk in the upper extremities and hyporeflexive in the lower extremities. She has a hesitant wide-based gait that requires a 2-person assist. The patient's laboratory values (reference ranges) show hemoglobin at 12.0 g/dL (12.0-15.5 g/dL); mean corpuscular volume, 87.8 fL (81.6-98.3 fL); sodium, 144 mg/dL (135-145 mg/dL); creatinine, 1.1 mg/dL (0.6-1.1 mg/dL); and serum urea nitrogen, 30 mg/dL (6-21 mg/dL). A deficiency in which of the following nutrients is the most likely cause of her symptoms?
a. Vitamin B_{12}
b. Vitamin D
c. Thiamine
d. Copper

III.13. A 32-year-old woman presents for a consultation, seeking bariatric surgery. She has a history of depression with a suicide attempt at 16 years of age, but she notes that she has been in therapy for sexual and physical abuse as a child. Her depression is now well controlled with a selective serotonin reuptake inhibitor. The patient also has history of sleep apnea and uses her continuous positive airway pressure machine regularly. In a review of her diet, she reports that she currently obtains more than 50% of her meals outside of the home because of her busy schedule. She has been making improved choices in her diet, including switching to diet soda with her meals, but also reports 5 or 6 servings of alcohol per week. Her fiancé notes that she had 2 citations for driving under the influence in the past year. Exercise is difficult for her because of erratic work hours. Her physical examination is unrevealing aside from a body mass index (BMI) of 38.7 kg/m^2. Which of these factors precludes her from moving ahead with bariatric surgery?
a. BMI less than 40 kg/m^2
b. History of depression with a previous suicide attempt
c. History of alcohol use
d. Lack of diabetes mellitus

III.14. A 71-year-old woman was admitted to the intensive care unit because of progressive respiratory failure due to moderate dyspnea, requiring mechanical intubation. Her medical history was clinically significant for severe chronic obstructive pulmonary disease and a 40 pack-year history of tobacco abuse. The patient's husband reported that she has lost more than 20% of her baseline weight over the past 3 months because of decreased oral intake. The patient's most recent body mass index (BMI) (1 week ago) from her primary care physician's office was 15 kg/m^2. Chest radiograph on admission showed a lobar pneumonia. Intravenous thiamine supplementation was given. Within 24 hours of admission, enteral nutrition was initiated through a recently placed nasogastric feeding tube, with a plan to achieve goal calories (50 kcal/h) within 72 hours. Electrolyte values were normal except for the potassium and phosphorus: serum potassium, 3.2 mmol/L (reference range, 3.6-5.2 mmol/L), and serum phosphorus, 2.5 mg/dL (reference range, 2.5-4.5 mg/dL). Serum laboratory values at 24 hours after initiation of enteral nutrition were potassium, 3.1 mmol/L, and phosphorus, 1.3 mg/dL. What is the most likely cause of the hypophosphatemia?
a. Hypoparathyroidism
b. Increased endogenous insulin and decreased glucagon
c. Vitamin D deficiency
d. Alcoholism

III.15. A 59-year-old man with familial dilated cardiomyopathy is being considered for heart transplant. He has impaired fasting glucose and diffuse thyromegaly. He has warm, moist, boggy hands; prominent eyebrows; minimal prognathism; and teeth marks on his tongue. Historically, the man may have had an increase in ring and shoe sizes, although not hat size. His thyroxin concentration was 6.9 mIU/L (reference range, 0.3-4.2 mIU/L); free thyroxine, 1.9 ng/dL (reference range, 0.9-1.7 ng/dL); and growth hormone (GH), 4.26 ng/mL (reference range, 0.01-0.97 ng/mL). The computed tomography image is shown in Figure III.Q15.

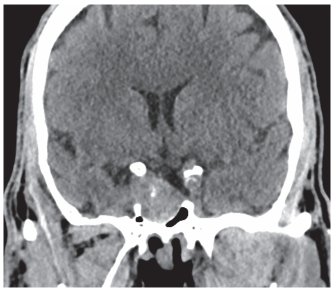

Figure III.Q15.

What should the next step in management be?

a. Radioactive iodine uptake and scan, followed by radioactive iodine therapy for thyrotoxicosis
b. Thyroid hormone replacement, starting at a small dose of 25 mcg daily
c. Pituitary surgery (or treatment with somatostatin analogue or pegvisomant if the patient is not a surgical candidate)
d. Testing for insulinlike growth hormone 1 (IGF-1), and GH after a 75-g dose of oral glucose

III.16. A healthy 32-year-old woman was found to have expressive galactorrhea (only on squeezing of the nipples) during breast examination. On direct questioning, she said she has not had spontaneous galactorrhea. She has no headaches and no suggestions of abnormalities in the field of vision. The rest of her examination, including field of vision, was normal. She has 3 children who are now 10, 8, and 7 years of age. She breastfed her children for about 6 to 8 months each. She currently takes conventional oral contraceptive pills (21 active and 7 inactive pills). Laboratory test results showed a serum prolactin of 34 ng/mL (reference range, 4.8-23.3 ng/mL); pregnancy test, negative; thyrotropin, 0.8 mcu/mL (reference range, 0.3-4.2 mcu/mL); free thyroxine, 1.0 ng/dL (reference range, 0.9-1.7 ng/dL); and serum creatinine, 0.9 mg/dL (reference range, 0.6-1.1 mg/dL). What should be the next step in her treatment?

a. Reassurance and observation
b. Bromocriptine
c. Cabergoline
d. Surgery if magnetic resonance imaging (MRI) of the pituitary shows adenoma

III.17. A 20-year-old man with type 1 diabetes mellitus has been seen by his physician for 6 years. He has had asthenia and nausea for the past 6 months and had a bout of vomiting after his noon meal, bringing him to the clinic. On inquiry, he tells his physician that he has had a substantial decrease in appetite. He has reduced his bolus doses of rapid-acting insulin with his decreasing carbohydrate intake. Despite this change, he has been having recurrent hypoglycemic events. He has lost about 12 pounds over the past 3 to 6 months. His pulse rate is 142 beats per minute. His blood pressure is supine at 92/68 mm Hg; when standing, it is 76/56 mm Hg. The patient's respiratory rate is 14 breaths/min. Examination shows a lean, ill-looking man with increased mucosal and palmar crease pigmentation and overall darkening of complexion. Laboratory test results show serum sodium, 134 mmol/L (reference range, 135-145 mmol/L); serum potassium, 5.4 mmol/L (reference range, 3.6-5.2 mmol/L); serum creatinine, 0.6 mg/dL (reference range, 0.6-1.1 mg/dL); serum beta-hydroxybutyrate, 0.3 mg/dL (reference range, <0.4 mg/dL); random plasma glucose, 89 mg/dL; hemoglobin A_{1c}, 6.5%; and thyroxin, 7.1 mIU/L (reference range, 0.3-4.2 mIU/L). A urinalysis reports glycosuria and is negative otherwise. What is the next best step in the care of this patient?

a. Dietary consultation and ensurance of 1,800 kcal in an American Diabetes Association diet with 50% to 60% calories as carbohydrates, 1 to 1.5 g of protein, and 20% of calories as healthy fat
b. Levothyroxine daily dosing at 75 mcg
c. Intravenous hydrocortisone 50 mg followed by 50 mg every 8 hours, with an 8 AM blood draw for cortisol and corticotropin (ACTH)
d. Immediate blood draw to test for cortisol and ACTH and administration of intravenous hydrocortisone 50 mg, followed by 50 mg every 8 hours

III.18. A 48-year-old overweight man is being seen by his physician for the inability to lose weight. He has started an aggressive exercise program and noted rapid development of palpitations. This has caused him to scale back on the exercise. During the examination, the man has a pulse of 88 beats per minute at rest and a body mass index of 31. He has generalized adiposity without stigmata of an endocrinopathy. He takes 81 mg of aspirin, 1 multivitamin, and 10 mg of biotin (for hair loss) daily. Initial tests are remarkable for a suppressed thyrotropin level of 0.05 mIU/L. What should be the next step in care management for this patient to determine whether he has hyperthyroidism?

a. Repeat thyroid test for thyrotropin, free thyroxine (T_4), and total triiodothyronine (T_3) after not taking biotin for 1 day.
b. Test for thyrotropin receptor antibodies (TRAbs).
c. Perform a thyroid ultrasonography looking for thyroid parenchyma echogenicity.
d. Perform a thyroid uptake test with radioactive iodine.

III.19. A 36-year-old woman seeks care for a pronounced decrease in overall energy associated with cold intolerance and sleepiness. She has a family history of Hashimoto thyroiditis that has affected her mother and her maternal grandmother. She follows a gluten-free diet because of her history of celiac disease. She takes no medications. On examination, the woman has a body mass index of 28, a pulse of 69 beats per minute, and blood pressure of 97/65 mm Hg. Her skin is dry, and her thyroid is slightly enlarged and firm without associated cervical adenopathy. Laboratory workup shows the following results: thyrotropin, 32 mIU/L; free thyroxine (T_4), 0.5 ng/dL (reference range, 0.9-1.7 ng/dL), and total triiodothyronine (T_3), 63 ng/dL (reference range, 80-200 ng/dL). Besides the initiation of levothyroxine (LT_4) therapy, what is the next best step in treating this patient?

a. Monitor the patient clinically and adjust LT_4 dosing until all symptoms have resolved.
b. Check concentration of thyroperoxidase antibodies.
c. Check morning cortisol concentration.
d. T_3 therapy to the LT_4 therapy.

III.20. A 59-year-old man is observed to have a thyroid nodule, discovered incidentally during ultrasonographic evaluation of the carotids. He has no personal or family history of thyroid disease, denies compressive symptoms of his neck, and has never been treated with radiation therapy. His thyroid examination is unremarkable, with a thyroid of normal size and consistency and without any palpable nodules. No cervical adenopathy is present. The rest of the physical examination is unremarkable. Thyrotropin is normal at 1.7 mIU/L. Thyroid ultrasonography performed after the carotid ultrasonography shows an 8-mm nodule (0.8 cm) in the central portion of the right thyroid lobe without extrathyroidal extension. The nodule is somewhat irregular and hypoechoic, more wide than tall, but with few hyperechoic specks. In the left thyroid lobe, a 4-mm pure cyst is identified. The rest of the examination is normal. The radiologist concludes that the right nodule shows moderate to high suspicion for malignancy and the left nodule low suspicion for malignancy. What is the next best step for thyroid management?

a. Fine-needle aspiration (FNA) of the right nodule
b. FNA of both nodules
c. Thyroid iodine scan
d. Ultrasonography of the thyroid in the next 6 to 12 months

Answers

III.1. Answer d.

This patient has mild hypercalcemia and a PTH level that is inappropriately elevated. To differentiate between primary hyperparathyroidism and familial hypocalciuric hypercalcemia (FHH), it is necessary to check a 24-hour urine collection for calcium and creatinine. If hypercalciuria is confirmed, then additional testing such as DXA should be ordered. If osteoporosis is confirmed, then parathyroid sestamibi scanning (preferred over ultrasonography) and surgical referral would be warranted. If his calcium to creatinine clearance ratio is less than 0.01, he has FHH and no further evaluation is warranted.

III.2. Answer c.

Nonadherence to therapy is the most likely cause of this patient's bone loss. Epidemiologic data show that approximately one-half of patients who are prescribed oral bisphosphonates discontinue them within 6 months, with other patients taking oral bisphosphonates either only intermittently or incorrectly. It is important to recognize that oral bisphosphonates are poorly absorbed (only approximately 1%) and must be taken correctly (with a glass of water first thing in the morning, without other medications or food for at least 30 minutes) to benefit patients. When a patient who received a prescription for an oral bisphosphonate has a documented decline in bone mineral density, an evaluation should be performed for both previously unidentified causes of bone loss and new causes. Thus, a careful review of interval history, performance of a physical examination, and review of medications and laboratory findings are essential. When taken correctly, oral bisphosphonates are highly effective at limiting bone loss. Thus, nonresponse to alendronate treatment is unlikely. Unrecognized malabsorption is unlikely given the patient's normal levels of 25-hydroxyvitamin D and of both serum and urine calcium. While technical error related to positioning can occur, it would be unlikely to occur at 2 independent sites (hip and spine).

III.3. Answer b.

Current guidelines recommend that for patients with asymptomatic Paget disease, a serum alkaline phosphatase level greater than 3 times the upper normal limit is an indication for treatment. Additional indications for treatment include involvement near a joint (to limit the risk of osteoarthritis), involvement of a weight-bearing bone (eg, leg, spine) to limit future fracture risk, or involvement of the skull (to limit the risk of cranial nerve impingement).

III.4. Answer b.

Diagnosis of diabetes mellitus requires a fasting plasma glucose ≥126 mg/dL, HbA_{1c} ≥6.5%, or a random glucose ≥200 mg/dL in the presence of symptoms of hyperglycemia. This patient has discordant results from fasting plasma glucose (does not meet the criterion) and HbA_{1c} (meets the criterion). In a clinical situation such as this, the test result above the diagnostic cut point should be repeated. Therefore, repeat HbA_{1c} would be the next best management choice in this patient. Oral glucose tolerance test is used to screen for diabetes during pregnancy and in people with cystic fibrosis. It is rarely, if ever, needed in other situations. Measurement of plasma insulin has no role in the diagnosis of diabetes, categorization of the type of diabetes, or establishment of the degree of insulin deficiency or insulin resistance in a person with diabetes.

III.5. Answer c.

Metformin is not contraindicated for this patient. Serum creatinine in isolation should not be used to decide whether metformin can be prescribed. According to the US Food and Drug Administration (FDA), metformin is contraindicated in patients with an eGFR <30 mL/min/1.73 m^2; moreover, starting metformin therapy in patients with an eGFR between 30 and 45 mL/min/1.73 m^2 is not recommended. For a patient such as this one, who was taking metformin and whose eGFR is now <45 mL/min/1.73 m^2, the FDA recommends assessment of the benefits and risks of continuing treatment. Metformin was rightly withheld at the time of iodinated contrast–medium imaging because his eGFR was between 30 and 60 mL/min/1.73 m^2. Reevaluation of eGFR (recommended at 48 hours after the imaging procedure) showed stability, and therefore metformin therapy can be restarted. Glyburide use is associated with increased cardiovascular mortality rate. It interferes with ischemic preconditioning. Such preconditioning occurs less often with glipizide; however, better options are available. Thiazolidinediones (eg, pioglitazone) increase the risk of a precipitated acute heart failure, especially for this patient, who appears to have fluid overload. Moreover, use of the DPP4 inhibitor saxagliptin has been shown to be associated with increased risk of heart failure. Therefore, both these agents are contraindicated. Liraglutide or empagliflozin should be considered for this patient. In addition to their use in improvement of glycemic control in adults with type 2 diabetes mellitus, these agents have been approved for people with established cardiovascular disease to reduce the risk of major adverse cardiovascular events (liraglutide) and cardiovascular death (empagliflozin). Before starting a glucagon-like peptide-1 receptor agonist (such as liraglutide), the patient should be asked about personal and family history of pancreatitis, pancreatic cancer, medullary thyroid cancer, and multiple endocrine neoplasia type 2, to ensure his history is negative for these conditions. In a randomized control trial, empagliflozin use was associated with a reduction of about 35% in hospitalization for heart failure. One could argue that empagliflozin is a better option for this patient; yet, his potassium level is high and empagliflozin can worsen hyperkalemia.

III.6. Answer d.

This obese young person is hospitalized with severe DKA (ie, anion gap >12 mmol/L, bicarbonate <10 mmol/L, and pH <7.0). The mainstay treatment of DKA is rehydration and provision of insulin to allow clearance of ketones. Normal saline is infused at 15 to 20 mL/kg body weight per hour, providing 1.0 to 1.5 L during the first hour, followed by a slower rate of about 500 mL per hour for second and third hours. He receives IV 0.45% saline at a rate of 250 to 500 mL per hour if the corrected serum sodium is normal or at an elevated level. When serum glucose decreases to less than 200 mg/dL, administration of normal saline is changed to 5% dextrose with 0.45% saline at a rate of 150 to 250 mL per hour. Intravenous bolus of regular insulin (0.1 U/kg body weight, once) is indicated if the infusion rate is <0.14 U/kg body weight per hour. This therapy is followed by IV insulin at a rate of 0.1 U/kg body weight per hour (or 0.14 U/kg body weight per hour if no bolus is given). The rate is reduced to 0.02 to 0.05 U/kg body weight per hour when glucose is less than 200 mg/dL. When glucose concentration is about 200 mg/dL, administration of IV dextrose with saline and IV insulin is adjusted to maintain blood glucose concentration between 150 and 250 mg/dL. Long-acting insulin (0.1-0.3 U/kg body weight per day) can be started soon after correction of shock and continued every 24 hours (glargine, degludec, or detemir) or twice a day (NPH).

With time, ketones will clear up. When β-hydroxybutyrate improves to a degree that the anion gap is closed, IV insulin administration is stopped, and bolus insulin (aspart, lispro, glulisine, or regular; 0.1-0.3 unit/kg body weight per day in 3 divided doses) is provided before each meal. The patient needs an infusion of potassium. Despite his normal to high-normal potassium level, the patient needs infusion of potassium because of his total-body potassium depletion. Insulin therapy, correction of acidosis, and volume expansion will decrease serum potassium concentration and will lead to hypokalemia if potassium replacement is not initiated. Bicarbonate therapy in DKA is controversial because it can cause paradoxical central nervous system acidosis, cerebral edema, hypokalemia, and decreased tissue oxygen availability. Randomized controlled trials show that bicarbonate therapy for diabetic ketoacidosis offers no advantage in improving cardiac or neurologic functions or in the rate of recovery of hyperglycemia and ketoacidosis. On the basis of expert opinion, the American Diabetes Association recommends provision of 100 mEq of bicarbonate for adults with DKA and a pH less than 6.9. This patient's phosphorus level is low, and it decreases with insulin therapy. However, randomized trials do not show any benefits effect of phosphate replacement on the clinical outcome in DKA. Moreover, it can cause hypocalcemia. The American Diabetes Association recommends provision of 20 to 30 mEq/L potassium phosphate added to replacement IV fluids if patient has cardiac dysfunction, anemia, or respiratory depression and for patients with serum phosphate concentration less than 1.0 mg/dL. The patient does not have a pH less than 6.9, phosphorus less than 1.0 mg/dL, cardiac dysfunction, anemia, or respiratory depression. In light of this clinical report, none of these therapies are indicated.

III.7. **Answer a.**

In a patient with clinically apparent Cushing syndrome, undetectable cortisol is sine qua non for Cushing syndrome caused by exogenous glucocorticoids. The patient is taking enteric glucocorticoids. These are absorbed in enough quantity to cause clinical features of Cushing syndrome. Therefore, screening for synthetic glucocorticoids is the next best step. Rarely, cyclical Cushing syndrome caused by ACTH-producing pituitary or extrapituitary tumors intermittently secreting excess ACTH can mimic the characteristics and laboratory findings of exogenous Cushing syndrome. In cyclic Cushing syndrome, the synthetic glucocorticoid screen is negative. Other tests are not indicated if the baseline cortisol is undetectable. Overnight dexamethasone, 24-hour urinary free cortisol, and late-night salivary cortisol are ordered if the baseline cortisol is not suppressed. Dehydroepiandrosterone-sulfate level is low in benign cortisol-producing adrenal tumors causing Cushing syndrome and is elevated in ACTH-dependent Cushing syndrome. ACTH stimulation test is used for the diagnosis of glucocorticoid insufficiency. This test is indicated when there is a clinical presentation of glucocorticoid insufficiency and should not be performed when the presentation is that of glucocorticoid excess.

III.8. **Answer c.**

Testosterone concentration has a diurnal variation. For confirmation that the patient has testosterone insufficiency, testosterone should be measured in the morning. If the result is abnormal again, testing for LH, FSH, and prolactin can then be ordered. Testosterone treatment is not started before testosterone deficiency confirmation on at least 2 separate occasions, both done in the morning. Inadequately treated obstructive sleep apnea will get worse with testosterone therapy, and it should be considered as a relative contraindication. Other contraindications for testosterone therapy include breast cancer, untreated prostate cancer, prostate-specific antigen (PSA) greater than 4 ng/mL (or PSA >3 ng/mL in African American men or men with first-degree relatives who had prostate cancer), hematocrit greater than 50%, severe lower urinary tract symptoms (American Urological Association/International Prostate Symptom Score >19), and uncontrolled or poorly controlled heart failure, or for men desiring fertility. Whereas weight control will benefit this young man, it is not of immediate concern.

III.9. **Answer b.**

The patient has symptoms suggestive of panhypopituitarism, likely from Sheehan syndrome. Treatment with hydrocortisone is relatively urgent but should be started after the blood draw for plasma cortisol and free T_4. Glucocorticoid insufficiency because of hypopituitarism does not require fludrocortisone. ACTH stimulation test will likely be normal because the onset of panhypopituitarism is relatively recent. Low TSH level does not always reflect thyrotoxicosis. In this case, the low TSH level is the cause of secondary hypothyroidism. Symptoms of inability to lactate, decreased appetite, and weight loss and test results of low prolactin, low sodium, and low-normal glucose levels suggest that the patient likely has panhypopituitarism. If her free T_4 level is low, she may require levothyroxine treatment. However, this therapy should not be started before replacement of glucocorticoids because it can precipitate adrenal crisis due to panhypopituitarism.

III.10. **Answer c.**

On the basis of the 2018 American College of Cardiology/American Heart Association guidelines, statins should be the therapy for a patient with diabetes mellitus. The primary goal of dyslipidemia management for this patient is reduction in her CVD risk. While fibric acid derivatives and niacin would help lower triglyceride and raise HDL-C levels, they are not effective agents for lowering CVD risk. Similarly, moderate-intensity statin therapy would not be as effective in CVD risk lowering as its high-intensity counterpart.

III.11. **Answer c.**

The goal of dyslipidemia management for this patient is LDL-C lowering and reduction in his risk of a future cardiovascular event, independent of LDL-C lowering. High-intensity statin therapy would be the most effective way of doing so. According to the 2018 American College of Cardiology/American Heart Association guidelines, patients with known atherosclerotic cardiovascular disease should be treated with high-intensity statin therapy. Red yeast rice, moderate-intensity statin therapy, and niacin therapy have not shown the same efficacy in cardiovascular disease risk reduction as high-intensity statin therapy.

III.12. Answer c.

This patient presents with recurrent nausea and vomiting along with neurologic symptoms 3 months after bariatric surgery because of thiamine deficiency. Thiamine is an essential coenzyme involved in glucose metabolism and the neurotransmitters acetylcholine and serotonin, and thiamine deficiency results in neurologic symptoms and mobility impairment. Absorption of thiamine, although not well understood, occurs mainly in the duodenum, with increased risk of deficiency after bariatric surgery in which the duodenum is bypassed. If thiamine deficiency or Wernicke encephalopathy is suspected, immediate administration of intravenous thiamine is recommended, given the lesser bioavailability of oral thiamine. Vitamin B_{12}, vitamin D, and copper deficiencies are not associated with the nausea, vomiting, and specific neurologic symptoms present in this patient.

III.13. Answer c.

The patient seems to have a significant history of alcohol use that may be underreported. The prevalence of alcohol use both before and after bariatric surgery is high, with some recent studies noting that almost 10% of patients may be abusing alcohol after gastric bypass. A number of factors, including change in anatomy that affects alcohol absorption and metabolism plus cross-addiction, have been implicated. Therefore, further evaluation of the patient's alcohol use is necessary, with consideration of referral to an addictions program or incorporation of addictions therapy in her ongoing care. The current indications for bariatric surgery include BMI greater than or equal to 40 or BMI greater than or equal to 35 and weight-related complications. This patient has a BMI greater than 35 with obstructive sleep apnea, thus she meets this indication. She has a history of suicide attempt; however, that was more than 10 years ago and she has been psychologically stable since the attempt. Certainly, her provider should confirm her stability and participation in ongoing therapy, but this would not preclude her from surgery, especially if the provider is willing to follow up and assist in post bariatric surgery care.

III.14. Answer b.

The patient is likely showing refeeding hypophosphatemia that, if left untreated, could progress to refeeding syndrome. During refeeding, insulin secretion increases and glucagon secretion decreases, which can lead to potentially fatal shifts in serum electrolyte levels. The patient had numerous major risk factors for refeeding syndrome: BMI less than 16, unintentional weight loss greater than 15% in the past 3 to 6 months, little nutritional intake for more than 10 days, and low levels of potassium, phosphate, or magnesium before feeding. In a randomized controlled trial of critically ill patients who had refeeding hypophosphatemia, those who were randomly assigned to decreased enteral feeding (<20 kcal/h) were more likely to be discharged alive than those who received goal feeding. The normal baseline phosphorus levels would make the possibility that hypoparathyroidism, vitamin D deficiency, and alcoholism unlikely as a cause of the hypophosphatemia in response to feeding. Hypoparathyroidism would likely have increased phosphorus and decreased calcium levels. Vitamin D deficiency would have hypocalcemia and decreased phosphorus.

III.15. Answer d.

The screening test for acromegaly is IGF-1, and the confirmatory test is GH concentration after a 75-g oral glucose load. GH secretion is pulsatile and episodic (from a normal pituitary and a pituitary adenoma). A nadir serum GH concentration of less than 1 mcg/L during the 2-hour 75-g oral glucose tolerance test excludes the diagnosis. The patient's IGF-1 was 798 ng/mL (reference range, 78-220 ng/mL), and his insulin-like growth factor binding protein 3 was 7.1 mcg/mL (reference range, 3.4-6.9 mcg/mL). Results from GH suppression with the glucose challenge are shown in Table III.A15.

Table III.A15 ●

Time, min	Test Value	
	Glucose, mg/dL	Growth Hormone, ng/mL
0	93	7.71
30	110	7.54
60	160	7.29
90	194	6.08
120	183	4.08

This outcome establishes the diagnosis of acromegaly. The patient has an elevated thyrotropin level, but his disorder is not hypothyroidism. Therefore, treatment with levothyroxine is not indicated. The patient has hyperthyroidism, evidenced by increased free thyroxine and despite the elevated thyrotropin level, because the latter is the cause of thyrotoxicosis, cosecreted with GH from the pituitary tumor. Investigations for and treatment of hyperthyroidism are not currently indicated because treatment of a GH-producing tumor takes care of the excess thyrotropin. Pituitary surgery, somatostatin analogue, or pegvisomant is an option but only after confirmation of acromegaly with documented elevation in IGF-1 level and demonstration of a lack of GH suppression on 75-g oral glucose challenge.

III.16. Answer a.

Physiologic causes of prolactin increase include pregnancy and stimulation of nipples during sexual intercourse. Lesions of the chest wall (including intrathoracic) and breast (including skin) can also cause hyperprolactinemia, as can primary hypothyroidism and renal failure. Multiple medications can cause increased prolactin concentration, including estrogens, dopamine receptor blockers (eg, phenothiazines), dopamine antagonists (eg, metoclopramide), alpha-methyldopa, cimetidine, opiates, antihypertensive medications, and antidepressants and antipsychotics. If the patient is symptomatic with spontaneous galactorrhea, the prolactin test can be repeated after discontinuation of the suspected medication for 3 days. MRI of the pituitary may be performed if the prolactin levels stay high after the suspected medicine has been discontinued. Expressive galactorrhea (only on squeezing of the nipples) can be normal in parous women. This patient likely has mild hyperprolactinemia from the oral estrogens in her birth control pills. Historically or on examination, there is no indication that the patient has a pituitary mass. First-line therapy with dopamine agonist to decrease prolactin concentrations is indicated for 1 or more of the following reasons: 1) to decrease the tumor size if the patient has a prolactinoma, 2) to restore estrogen concentration to avoid the long-term consequences of hypogonadism (eg, osteoporosis, vaginal dryness), and 3) to address spontaneous socially awkward hyperprolactinemia. Cabergoline is preferred over bromocriptine because it has greater efficacy in normalizing prolactin concentrations, as well as a higher frequency of pituitary tumor shrinkage. Dopamine agonists are often not tolerated because of nausea, fatigue, asthenia, dizziness, and headaches. Gastrointestinal tract adverse effects can be reduced with intravaginal administration of a dopamine agonist. Transsphenoidal surgery is reserved for symptomatic patients with prolactinomas who cannot tolerate adequate doses of cabergoline or are not responsive to the best tolerated doses of dopamine agonists. For patients for whom surgical treatment fails or who harbor aggressive or malignant prolactinomas, radiation therapy and temozolomide therapy are further options.

III.17. Answer d.

Addison disease occurs more commonly in people with other autoimmune conditions, including type 1 diabetes mellitus. This patient has tachycardia and hypotension in addition to hyperpigmentation. When there is a high index of suspicion, an elevated serum potassium level is a better predictor of Addison disease than a decreased serum sodium level. Urgent initiation of treatment is indicated. However, blood for plasma cortisol and ACTH has to be drawn before provision of hydrocortisone. In light of the urgency of treatment, waiting until the next morning for blood draw followed by treatment would be unsafe. Untreated Addison disease can be associated with an elevated thyrotropin level. This elevation does not imply hypothyroidism that requires treatment. Levothyroxine treatment can increase cortisol metabolism and therefore can precipitate life-threatening adrenal crisis in such a person. Dietary consultation will not address the problem of anorexia. Additionally, there is no "American Diabetes Association diet," and there is no universal ideal macronutrient distribution for persons with diabetes.

III.18. Answer a.

Biotin is known to interact with the biotinylation reaction used in a number of immunoassays, including some assays for thyrotropin, free T_4, and TRAbs. To avoid such interference, biotin should be discontinued for a minimum of 12 hours. If the interaction is still present, it can mimic Graves disease (suppressed thyrotropin and elevated T_4 and TRAb levels). Similarly, TRAb testing is ineffective if biotin is not eliminated. Thyroid ultrasonography (particularly for echogenicity as opposed to vascularity) and thyroid uptake test are unable to differentiate between normal thyroid and a thyroid affected by Graves disease. Thyroid echogenicity is not known to be affected by hyperthyroidism. Thyroid uptake is interpretable only in the clinical setting of a reliable thyrotropin measurement, since the uptake depends on the thyrotropin level. Thus, a thyroid uptake test with radioactive iodine cannot help in the diagnosis of hyperthyroidism until the biotin interference is eliminated.

III.19. Answer c.

The next best step is to check the morning cortisol concentration. This patient has an autoimmune form of hypothyroidism, Hashimoto thyroiditis, possibly as part of an autoimmune polyglandular syndrome. It is important to now assess adrenal function since hypothyroidism prolongs the half-life of cortisol. Thereby, it can mask adrenal insufficiency to some extent, and normalizing thyroid levels can lead to a rapid decline in cortisol levels with overt clinical manifestations of adrenal insufficiency. Adjustment of the treatment of hypothyroidism should be guided by biochemical assessment, with the goal of a normal thyrotropin value as opposed to symptoms control, since symptoms of hypothyroidism are nonspecific and can be multifactorial. Measurement of thyroperoxidase antibodies is not necessary because thyroid autoimmune dysfunction is likely and thyroperoxidase antibodies titer would not affect therapy. Combination T_4 and T_3 therapy is not the standard of treatment and should not be the first choice for hypothyroidism treatment, even when adrenal function is normal.

III.20. Answer d.

The next step is to repeat ultrasonography of the thyroid in 6 to 12 months. This nodule measures 10 mm or less, and if it were a papillary thyroid cancer, the natural history of the lesions would be good, with about 90% of cases being stable at 20 years of follow-up. Therefore, FNA is no longer recommended for lesions 10 mm or more, and observation is an appropriate route of management, particularly after age 40 years (lower likelihood of metastatic spread). An FNA of the right nodule is no longer the first choice unless modifying factors are present (eg, the nodule has an extrathyroidal extension, the nodule is associated with suspicious cervical adenopathy). FNA for a cystic nodule is completely unnecessary. In the clinical setting of a normal thyrotropin level, a thyroid iodine scan is not useful, and the possibility of a toxic nodule has been excluded through the thyrotropin value.

Section IV

Gastroenterology and Hepatology

19 Colonic Disorders

JOHN B. KISIEL, MD

Inflammatory Bowel Disease

Definitions

Inflammatory bowel disease refers to 2 disorders of unknown cause: ulcerative colitis and Crohn disease. Other possible causes of inflammation, especially infection, should be excluded before making the diagnosis of inflammatory bowel disease. The presence of chronic inflammation on biopsy is the key factor for diagnosing inflammatory bowel disease.

Ulcerative colitis is mucosal inflammation involving only the colon. **Crohn disease** is transmural inflammation that can involve the gastrointestinal tract anywhere from the esophagus through the anus. The rectum is involved in about 95% of patients with ulcerative colitis and in only 50% of patients with Crohn disease. Ulcerative colitis is a continuous inflammatory process that extends from the anal verge to the more proximal colon (depending on the extent of the inflammation). Crohn disease is segmental inflammation in which inflamed areas alternate with virtually normal areas. Ulcerative colitis usually presents with frequent, bloody bowel movements with minimal abdominal pain, whereas Crohn disease presents with fewer bowel movements, less bleeding, and, more commonly, abdominal pain. Crohn disease is associated with fibrotic stricturing behavior, which leads to obstruction. Penetrating manifestations of Crohn disease include intestinal fistulas, fistulas from the intestine to other organs, and perianal disease. Ulcerative colitis does not form fistulas, and perianal disease is uncommon. Strictures of the intestine are common with Crohn disease but rare in ulcerative colitis (when they are present, they suggest cancer).

Key Definitions

Inflammatory bowel disease: *inflammatory intestinal disease with an unknown cause; includes ulcerative colitis and Crohn disease.*

Ulcerative colitis: *mucosal inflammation that involves only the colon.*

Crohn disease: *transmural inflammation that can involve any portion of the gastrointestinal tract (from the esophagus through the anus).*

Extraintestinal Manifestations

Arthritis occurs in 10% to 20% of patients with inflammatory bowel disease, usually as monarticular or pauciarticular involvement of large joints. Peripheral joint symptoms mirror bowel activity: Joint symptoms flare when colitis flares, and joint symptoms improve as colitis improves. When axial joint symptoms develop, such as those of ankylosing spondylitis (which has a relationship with HLA-B27) and sacroiliitis, they are usually progressive and do not improve when colitis improves.

Skin lesions occur in 10% of patients. The 3 lesions seen most commonly are erythema nodosum, pyoderma gangrenosum, and aphthous ulcers of the mouth. Erythema nodosum and aphthous ulcers usually improve with treatment of colitis, whereas pyoderma gangrenosum has an independent course. Severe, refractory skin disease is an indication for surgical treatment.

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Eye lesions occur in 5% of patients. The lesion is usually episcleritis or uveitis (or both). Episcleritis usually mirrors inflammatory bowel disease activity, but uveitis does not. Episcleritis typically presents with a painless red eye, whereas uveitis often presents with a painful red eye. Uveitis is an indication for emergent ophthalmologic evaluation.

Renal lithiasis occurs in 5% to 15% of patients. In Crohn disease with malabsorption, calcium oxalate stones occur. In ulcerative colitis, uric acid stones due to dehydration and loss of bicarbonate in the stool lead to acidic urine.

Liver disease occurs in 5% of patients. Primary sclerosing cholangitis is more common in ulcerative colitis than in Crohn disease. If the alkaline phosphatase level is increased in a patient with inflammatory bowel disease, the evaluation for primary sclerosing cholangitis may include magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, and possibly liver biopsy.

Indications for Colonoscopy

Colonoscopy is indicated for evaluating the extent of the disease, performing biopsies, and evaluating strictures. It is also indicated for distinguishing Crohn disease from ulcerative colitis. Another indication for colonoscopy is surveillance for dysplasia or cancer by targeted biopsy of dye-enhanced lesions (chromoendoscopy) or by random surveillance biopsies (typically, a total of 32 biopsies) in patients who have had ulcerative colitis (involving colon proximal to the rectum) or Crohn colitis for more than 8 years. Patients who have ulcerative colitis limited to the rectum (ulcerative proctitis) are not at increased risk for dysplasia and colon cancer; they do not require surveillance colonoscopy.

Toxic Megacolon

Patients with active inflammation should avoid potential precipitants of toxic megacolon, such as opioids, anticholinergic agents, hypokalemia, and barium enema. If toxic megacolon is suspected on the basis of abdominal pain, sepsis, or abnormal imaging findings, patients should be hospitalized for supportive care, exclusion or treatment of infection with *Clostridioides difficile* (formerly known as *Clostridium difficile*), and urgent colorectal surgery consultation.

Treatment of Ulcerative Colitis

Sulfasalazine and other aminosalicylates can induce remission in 80% of patients with mild or moderate ulcerative colitis and are effective maintenance therapy for 50% to 75% of patients with ulcerative colitis. The active agent of sulfasalazine, 5-aminosalicylic acid (5-ASA), is bound to sulfapyridine (the vehicle). Colonic bacteria break the bond and release 5-ASA, which is not absorbed but stays in contact with the mucosa and exerts its anti-inflammatory action. The efficacy of 5-ASA may be related to its ability to inhibit the lipoxygenase pathway of arachidonic acid metabolism or to function as an oxygen free-radical scavenger. It is effective in acute disease and in maintaining remission.

The 5-ASA drugs may be delivered to the intestine in various ways. They eliminate sulfa toxicity but are more expensive than sulfasalazine. Two of these drugs are mesalamine and olsalazine. Mesalamine can be given topically (Rowasa suppositories and Rowasa enema) or orally (Asacol, which is 5-ASA coated with an acrylic polymer that releases 5-ASA in the terminal ileum, and Pentasa, which has an ethylcellulose coating that releases 50% of the 5-ASA in the small bowel). Olsalazine consists of 2 molecules of 5-ASA conjugated with each other. Bacteria break the bond, which releases 5-ASA into the colon.

Aminosalicylates are used for mild to moderately active ulcerative colitis. Topical forms are useful for proctitis or left-sided colitis; systemic forms are used for pancolitis. Of the patients who do not tolerate sulfasalazine, 80% to 90% tolerate oral 5-ASA preparations.

Generally, 5-ASA drugs are very well tolerated. About 10% of patients may experience paradoxical worsening of colitis. Rare adverse effects also include reversible sterility in men, malaise, nausea, pancreatitis, rashes, headaches, hemolysis, impaired folate absorption, hepatitis, and aplastic anemia. These effects may be related to the sulfapyridine moiety and occur in 30% of patients who take sulfasalazine. Interstitial nephritis can occur with any of the 5-ASAs. Patients taking 5-ASAs should be monitored by assessing complete blood count, liver injury markers, and serum creatinine values annually. Aminosalicylates have not been shown to be beneficial for the treatment of Crohn disease.

Topical corticosteroid preparations may be used for patients with active disease that is limited to the distal colon, although these are less effective than topical aminosalicylates. Oral corticosteroids should be added to the regimen for patients with more proximal disease if oral aminosalicylates do not control the symptoms. Up to 50% of the dose can be absorbed. Oral preparations (prednisone 40 mg daily, *extended-release* budesonide 9 mg daily) are indicated in active pancolonic disease that is of moderate severity and is unresponsive to aminosalicylates. Prednisolone, the active metabolite, is the preferred form of drug for patients with cirrhosis (these patients may not be able to convert inactive prednisone to prednisolone). For patients who have a prompt response to oral corticosteroids, the dose may be tapered gradually at a rate not to exceed a 5-mg decrease in the total dose every 7 days. Total duration of systemic corticosteroid therapy should be limited to 12 weeks or less, and steroid-sparing maintenance therapies should be instituted early in the course of the corticosteroid taper. Steroid-sparing therapies include the 5-ASAs, thiopurines, or biologic drugs. Patients with disease flares within 90 days of taper completion or who require multiple tapers per year are not receiving adequate steroid-sparing maintenance therapy.

In severely ill patients, intravenous preparations should be given (methylprednisolone, 40-60 mg daily) for 3 to 5 days. If improvement occurs at that time, therapy should be converted to oral corticosteroids (40 mg daily). If improvement does not occur, infliximab (see Treatment of Crohn Disease subsection) may be considered for induction of remission. If there is no improvement, surgical intervention (colectomy) is required. Because corticosteroids are not thought to prevent relapse, they should not be prescribed after the patient has complete remission and is free of symptoms.

Additional biologic agents approved by the US Food and Drug Administration (FDA) for outpatient treatment of moderate to severe ulcerative colitis include adalimumab, golimumab, and vedolizumab; these medicines have not been demonstrated to induce remission in hospitalized patients who do not respond to intravenous corticosteroids.

Total parenteral nutrition does not alter the clinical course of an ongoing episode of symptoms. Indications for its use include severe dehydration and cachexia with marked fluid and nutrient deficits, excessive diarrhea that has not responded to standard therapy for ulcerative colitis, and debilitation in patients undergoing colectomy. Use of opioids and anticholinergic agents should be limited in ulcerative colitis because they can contribute to the development of toxic megacolon. Narcotic use is an independent risk factor for death in patients with ulcerative colitis and Crohn disease.

Surgical treatment is curative in ulcerative colitis. Indications for colectomy include severe intractable disease, acute life-threatening complications (perforation, hemorrhage, or toxic megacolon unresponsive to treatment), symptomatic colonic stricture, and suspected or documented colon cancer. Other indications are intractable moderate or severe colitis, refractory uveitis or pyoderma gangrenosum, growth retardation in children, cancer prophylaxis, or inability to taper a regimen to low doses of corticosteroid (ie, <15 mg daily) over 2 to 3 months despite use of steroid-sparing therapies.

Treatment of Crohn Disease

Considerable controversy exists regarding the role of aminosalicylates for the treatment of Crohn disease. A recent Cochrane systematic review failed to find superiority of several 5-ASA formulations over placebo or corticosteroids for the end points of clinical response or induction of remission. In patients who have undergone surgery to induce remission of Crohn disease, 5-ASA products have been shown to prevent postoperative recurrence but are probably less effective than thiopurines or infliximab.

The use of corticosteroids is discussed above (see Treatment of Ulcerative Colitis subsection). Corticosteroids have the fastest onset of action of any therapies for Crohn disease and, thus, are frequently used during acute exacerbations. Of the corticosteroid formulations, *enteric-coated* budesonide is favored for the treatment of mild to moderate distal small-bowel and proximal colonic Crohn disease because it has limited systemic toxicity owing to first-pass hepatic metabolism. Enteric-coated budesonide is ineffective for more distal colonic Crohn disease; extended-release budesonide is FDA approved only for ulcerative colitis.

Azathioprine and 6-mercaptopurine (the active metabolite of azathioprine) have steroid-sparing effects. These immunomodulating medications are effective for maintaining remission but not for treating acute disease flares because they have a gradual onset of action (6-8 weeks). Their use should be reserved for patients who are taking corticosteroids for active disease and whose corticosteroid dose needs to be decreased (or a given dose needs to be maintained because of worsening disease activity). Thiopurines are generally well tolerated, but nausea and myalgias are commonly reported. Rare but serious adverse effects include drug-induced liver injury, pancreatitis, bone marrow suppression, and fever. These drugs are also strongly associated with increased risk of lymphoma and nonmelanoma skin cancers. Dosing is weight based after ascertainment of thiopurine methyltransferase activity. Complete blood count and liver injury markers are typically checked every 3 months for patients taking stable doses.

Infliximab is a chimeric monoclonal antibody directed against tumor necrosis factor α (anti-TNF). This intravenously administered anti-inflammatory agent is effective in treating moderately or severely active Crohn disease and ulcerative colitis refractory to conventional therapy and in treating fistulizing Crohn disease. Infliximab is a steroid-sparing agent that is effective in maintaining remission of Crohn disease. Infusion reactions (pruritus, dyspnea, or chest pain) may occur. The drug is associated with an increased risk of infection, including perianal abscesses, tuberculosis, and other respiratory infections. Rarely, subsequent infusions of infliximab may be associated with delayed hypersensitivity reactions. Infliximab is frequently used in combination with thiopurine therapy because combination therapy has been demonstrated to be superior to the use of either drug alone (SONIC trial).

Other anti-TNFs include adalimumab and certolizumab pegol; the subcutaneous injectable forms of these drugs are increasingly used because of their lower cost of administration.

Anti-integrin biologic agents for Crohn disease include natalizumab and vedolizumab. Natalizumab targets the $\alpha4\beta1$ integrins found on most endothelial surfaces, including brain vessels. In postmarket follow-up, natalizumab was associated with a significant increase in progressive multifocal leukoencephalopathy, a potentially fatal demyelinating disease associated with JC virus reactivation. Vedolizumab targets the $\alpha4\beta7$ integrins, which are not found in the brain endothelium. To date, progressive multifocal leukoencephalopathy has not been reported in patients receiving vedolizumab. Vedolizumab has been FDA approved for both Crohn disease and ulcerative colitis. The order of use of vedolizumab or anti-TNF therapy in patients with disease severe enough to warrant biologic therapy is currently unclear.

Most recently, ustekinumab, an anti-interleukin 12/23 monoclonal antibody, was approved for Crohn disease. This drug is delivered by a weight-based loading infusion, followed by injectable maintenance therapy (90 mg) every 8 weeks. Although this medicine appears highly safe and effective for moderate-to-severe Crohn disease, it is seldom used as a first-line biologic, primarily because of its high cost.

Although no laboratory monitoring for toxicity is needed for biologic therapies, patients started on biologics should be screened for latent tuberculosis and hepatitis B infection. Those with latent tuberculosis require at least the first month of antimicrobial therapy before starting the biologic. Those with hepatitis B infection, chronic carrier status, or even natural immunity, should receive antiviral therapy while taking biologics. Those with vaccination-induced immunity should not.

Bowel rest does not have a role in achieving remission in Crohn disease. Providing adequate nutritional support, however, does help facilitate remission; any form of nutritional support is acceptable as long as the amount is adequate. Adequate nutrition can be essential in maintaining growth in children who have severe Crohn disease.

If a patient with Crohn disease is undergoing exploratory surgery for presumed appendicitis, the acute ileitis should be left alone (in many of these patients, chronic Crohn disease does not develop). Appendectomy can be performed if the cecum and appendix are free of disease. Of the patients with Crohn disease who have surgical treatment, 70% to 90% require reoperation within 15 years (many within the first 5 years after the initial operation). The anastomotic site is the most likely location for recurrence of disease. Postoperative prophylaxis should be strongly considered for patients with 1 or more of the risk factors for recurrence, which include young age, smoking, and penetrating disease phenotype. Indications for surgical treatment include intractable symptoms, acute life-threatening complications, obstruction, refractory fistulizing disease, abscess formation, and malignant processes. A summary of therapies for ulcerative colitis and Crohn disease is given in Table 19.1.

Microscopic Colitis

The so-called third inflammatory bowel disease, microscopic colitis, is divided into 2 histologic subtypes: lymphocytic colitis, defined by intraepithelial lymphocytic infiltrate (>20 per high-power field), and collagenous colitis, characterized by the presence of a subepithelial collagen band at least 10 µm thick. Both subtypes are associated with chronic, secretory, watery diarrhea; the presentation is most common among middle-aged women. By definition, the colon is endoscopically normal, and diagnosis must be established with random biopsies. The disease has been associated with medications, specifically nonsteroidal anti-inflammatory drugs, proton-pump inhibitors, serotonin reuptake inhibitors, and statins, among others; neither mechanisms nor causal relationships are clear. Microscopic colitis is also associated with autoimmune diseases; affected persons should be screened for celiac disease. Stool pathogens, most importantly *C difficile*, should also be excluded.

Symptoms can be managed with loperamide and by discontinuing potentially offending medications, if possible. For those with persistent or severe symptoms, enteric-coated budesonide (9 mg daily for 4 weeks) can be added. If there is good response, budesonide can be tapered at a rate of 3 mg per week. Relapses are common. Low-dose maintenance budesonide is superior to placebo and may improve quality of life in patients with corticosteroid-dependent disease but has the potential for long-term adverse effects. There is limited evidence to support the use of cholestyramine and bismuth subsalicylate; mesalamine is most likely not effective.

KEY FACTS

✓ Extraintestinal manifestations of inflammatory bowel disease—
- arthritis in 10%-20% of patients (usually monarticular or pauciarticular involvement of large joints)
- when present, axial joint symptoms (eg, from ankylosing spondylitis or sacroiliitis) are usually progressive and do not improve when colitis improves
- skin lesions in 10% of patients (eg, erythema nodosum, pyoderma gangrenosum, and aphthous ulcers of the mouth)

✓ Colonoscopy for inflammatory bowel disease—
- to evaluate extent and severity of disease
- to perform biopsies
- to evaluate strictures and filling defects
- to assess mucosal response to changes in therapy

✓ Cross-sectional imaging by computed tomography or magnetic resonance enterography—
- to exclude small bowel disease in patients known to have colonic inflammatory bowel disease
- to evaluate disease extent in those known to have small bowel Crohn disease
- to exclude stricturing or penetrating complications in small bowel Crohn disease
- to monitor response to therapy

✓ Treatment of ulcerative colitis with sulfasalazine and other aminosalicylates—
- induces remission in 80% of patients with mild or moderate ulcerative colitis
- is effective maintenance therapy for 50%-75% of patients with ulcerative colitis

✓ Treatment of Crohn disease—
- corticosteroids for acute exacerbation only
- thiopurine monotherapy appropriate for low-risk or mild Crohn disease
- aminosalicylate therapy should be avoided

✓ Biologics (monoclonal antibody therapies)—
- intravenous or injectable
- effective in treating moderately or severely active Crohn disease and ulcerative colitis refractory to conventional therapy
- effective in treating fistulizing Crohn disease
- more effective when used in combination with thiopurine

Table 19.1 • Simplified Overview of Therapies for Inflammatory Bowel Disease

Disease	Induction of Remission	Maintenance of Remission
Ulcerative colitis		
Mild-moderate[a]	5-ASA	5-ASA
Moderate-severe[b]	Corticosteroid taper	5-ASA with or without thiopurines Biologic monotherapy (infliximab, adalimumab, golimumab, vedolizumab) Combination therapy with biologic and thiopurine[c]
Crohn disease		
Low-risk[d]	Corticosteroid taper	Thiopurine monotherapy[e]
Moderate-high-risk	Corticosteroid taper	Biologic monotherapy (infliximab, adalimumab, certolizumab, vedolizumab, ustekinumab) Combination therapy with biologic and thiopurine[c]

Abbreviation: 5-ASA, 5-aminosalicylic acid.

[a] For patients with rectal or sigmoid activity, topical 5-ASA therapy and corticosteroid enemas can be used as monotherapy or in combination with oral delivery.

[b] Severity is defined by symptoms and endoscopic disease activity.

[c] Combination therapy may be initiated with the first use of a biologic agent and should be strongly considered in patients for whom other biologics have failed in the past.

[d] Low risk of complications or long-term debility is suggested by age older than 30 years at initial diagnosis, limited anatomic involvement, lack of perianal or severe rectal disease, presence of superficial ulcers only, lack of prior surgical resection, and lack of stricturing or penetrating behavior. Presence of any of these features suggests high current or prior disease burden, which increases the long-term complication risk.

[e] Methotrexate may be used if patients are poorly tolerant of thiopurines.

Miscellaneous Infectious Causes of Colonic Disorders

Amebic Colitis

The colon is the usual initial site of amebic colitis. Symptoms vary from none to explosive bloody diarrhea with fever, tenesmus, and abdominal cramps. Proctoscopy shows discrete ulcers with undermined edges and normal adjacent mucosa. If exudate is present, it should be swabbed to make wet mounts to search for trophozoites. The indirect hemagglutination assay is useful for diagnosing invasive disease. Radiography shows concentric narrowing of the cecum in 90% of patients. Amebic colitis is treated with metronidazole. The only pathogenic ameba in humans is *Entamoeba histolytica*.

Tuberculosis

Presenting symptoms of tuberculosis may include diarrhea, a change in bowel habits, and rectal bleeding. The clinical presentation may closely resemble Crohn disease but can also include peritonitis with ascites or hepatic involvement. The ileocecal area is the most commonly involved site. Radiography shows ulceration and a contracted cecum and ascending colon. Proctoscopy may show an ulcerating mass. Biopsy samples stained with Ziehl-Neelsen stain are positive for acid-fast bacilli. Mycobacterial culture and nucleic acid amplification testing may also aid in diagnosis. If tuberculosis is diagnosed, HIV infection should also be excluded. Cases may be associated with pulmonary or miliary tuberculosis but may also occur as a result of ingested organisms. Antituberculous therapy for intestinal disease is similar to that for pulmonary disease.

Streptococcus bovis Endocarditis

Streptococcus bovis endocarditis is associated with colonic disease (diverticulosis or cancer). The colon should be evaluated.

Pseudomembranous Enterocolitis

Pseudomembranous enterocolitis is a necrotizing inflammatory disease of the intestines characterized by the formation of a membranoid collection of exudate overlying a degenerating mucosa. Precipitating factors include colon obstruction, uremia, ischemia, intestinal surgery, and all antibiotics (except vancomycin).

Antibiotic Colitis

The symptoms of antibiotic colitis are fever, abdominal pain, and diarrhea (mucus and blood), which usually occur 1 to 6 weeks after the initiation of antibiotic therapy. Sigmoidoscopy shows pseudomembranes and friability. Biopsy specimens show inflammation and microulceration with exudation. The condition usually remits, but it recurs in 15% of patients. Complications include perforation and megacolon. The pathogenesis begins with the antibiotic altering the colonic flora, which results in an overgrowth of *C difficile*. The toxin produced by *C difficile* is cytotoxic, causing necrosis of the epithelium and exudation (pseudomembranes). Diagnosis is based on a stool toxin assay. ELISA (enzyme-linked immunosorbent assay)-based stool testing has a sensitivity of 70% when only 1 stool sample is examined. The sensitivity increases to 90% when 2 stool samples are examined. Polymerase chain reaction (PCR)-based stool testing has a sensitivity of 95% when only 1 stool sample is examined. Proctoscopic findings may be normal or show classic pseudomembranes. The treatment is to discontinue the use of antibiotics and provide general supportive care (eg, fluids). Antimotility agents should be avoided. Metronidazole (500 mg 3 times daily) is 80% effective and inexpensive and is recommended for patients with mild disease (leukocyte count $<15.0\times10^9$/L and normal serum creatinine value). Vancomycin (125 mg 4 times daily) is recommended for patients with more severe disease (leukocyte count $\geq15.0\times10^9$/L and increased serum creatinine value). For a first recurrence, the same antibiotic can be used, or the drug can be switched. For multiple recurrences, cholestyramine should be added and the course of treatment with antibiotics prolonged.

KEY FACTS

✓ Amebic colitis—colon is the usual initial site

✓ Colonic disease in patients with tuberculosis—

- diarrhea, change in bowel habits, and rectal bleeding
- ileocecal area is the most commonly involved site

✓ Antibiotic colitis—fever, abdominal pain, and diarrhea, usually 1-6 weeks after initiation of antibiotic therapy

Radiation Colitis

Irradiation injury usually affects both the colon and the small bowel. Endothelial cells of the small submucosal arterioles are radiosensitive and respond to large doses of irradiation by swelling, proliferating, and undergoing fibrinoid degeneration. The result is obliterative endarteritis.

Acute disease occurs during or immediately after irradiation; the mucosa fails to regenerate, and there is friability, hyperemia, and edema. *Subacute disease* occurs 2 to 12 months after irradiation. Obliterative endarteritis produces progressive inflammation and ulceration. *Chronic disease* consists of fistulas, abscesses, strictures, and bleeding from intestinal mucosal vessels. Predisposing factors include total irradiation dose of 40 to 50 Gy, previous chemotherapy, adhesions, previous surgical procedure, pelvic inflammatory disease, older age, and other diseases that produce microvascular insufficiency (eg, hypertension, diabetes mellitus, atherosclerosis, and heart failure) because they accelerate the development of vascular occlusion. The elderly are more susceptible. Radiography during acute disease shows fine serrations of the bowel, and radiography during chronic disease shows stricture of the rectum, which is involved most commonly. Endoscopy shows atrophic mucosa with telangiectatic vessels. Endoscopic coagulation is effective treatment for bleeding, but surgery may be required for fistulas, strictures, or abscesses.

Ischemia

Review of Vascular Anatomy

The *celiac trunk* supplies the stomach and duodenum. The *superior mesenteric artery* supplies the jejunum, ileum, and right side of the colon. The *inferior mesenteric artery* supplies the left side of the colon and rectum.

Acute Ischemia

The symptoms of acute ischemia are sudden and severe abdominal pain, vomiting, and diarrhea (with or without blood). Early in the course of ischemia, physical examination findings are normal despite reports of severe abdominal pain. Risk factors include severe atherosclerosis, congestive heart failure, atrial fibrillation (source of emboli), hypotension, and oral contraceptives.

There are several acute ischemic syndromes. *Acute mesenteric ischemia* is due to embolic obstruction of the superior mesenteric artery in 80% of patients. Most emboli (95%) lodge in this artery because of laminar flow, vessel caliber, and the angle at which it emerges from the aorta. This syndrome may result in a loss of small bowel and produce short-bowel syndrome. Radiography shows ileus, small-bowel obstruction, and, later, gas in the portal vein. The treatment is embolectomy.

Key Definitions

Ischemic colitis: *inflammation of the colon due to a transient decrease in perfusion pressure with chronic, diffuse mesenteric vascular disease.*

Ischemic colitis is due to a transient decrease in perfusion pressure with chronic, diffuse mesenteric vascular disease. This decrease occurs in severe dehydration or shock and results in ischemia of the gastrointestinal tract. It commonly involves areas of the colon between adjacent arteries (ie, “watershed areas”) such as the splenic flexure and the rectosigmoid. Patients with this syndrome have abdominal pain and rectal bleeding. The characteristic radiographic feature is thumbprinting of watershed areas. The treatment is supportive, with administration of intravenous fluids to maintain adequate tissue perfusion, and consideration of antibiotics if clinically significant leukocytosis or fever is present. If the condition deteriorates, surgical resection may be necessary.

Nonocclusive ischemia is due to poor tissue perfusion caused by inadequate cardiac output. It can involve both small and large bowels. Its distribution does not conform to an area supplied by a major vessel. It occurs in patients with hypovolemic states, cardiac failure, or anoxia and in patients who have other forms of distributive shock.

Chronic Mesenteric Ischemia (Intestinal Angina)

Chronic mesenteric ischemia is uncommon. Symptoms include postprandial pain and fear of eating, with secondary weight loss. At least 2 of 3 major splanchnic vessels must be occluded to make the diagnosis. Chronic mesenteric ischemia is associated with hypertension, diabetes mellitus, and atherosclerosis. An abdominal bruit is a clue to the diagnosis. Noninvasive imaging may be performed, including duplex ultrasonography or computed tomography or magnetic resonance angiography. The primary treatment options are angiography with possible stent placement or surgical revascularization.

Occlusion of the superior mesenteric vein accounts for approximately 10% of the cases of bowel ischemia. Risk factors include hypercoagulable states such as polycythemia vera, liver disease, pancreatic cancer, intra-abdominal abscess, and portal hypertension. The presentation is abdominal pain that gradually becomes severe. Diagnosis is based on noninvasive imaging studies such as duplex ultrasonography or computed tomography.

Irritable Bowel Syndrome

The term *irritable bowel syndrome* is used for symptoms that are presumed to arise from the small and large intestines. It refers to a well-recognized complex of symptoms resulting from interactions of the intestine, the psyche, and, possibly, luminal factors. Most patients have abdominal pain that is relieved with defecation or associated with a change in the frequency or consistency of the stool. Major subtypes are diarrhea predominant, constipation predominant, or mixed type. On average, pain should be present for at least 1 day per week for the past 3 months, and symptom onset must be at least 6 months before diagnosis. Other associated symptoms include abdominal bloating and passage of excessive mucus with the stool. So-called alarm features, such as anemia, fever, unintentional weight loss, gastrointestinal tract bleeding, nocturnal pain/defecation, and fecal incontinence should be absent.

The diagnosis of irritable bowel syndrome is confirmed by an appropriate medical evaluation that does not identify an organic illness. If localizing signs or symptoms are elicited, limited, directed diagnostic work-up is appropriate. Patients who have upper abdominal discomfort and bloating may require an ultrasonographic examination of the abdomen and esophagogastroduodenoscopy. Patients who have lower abdominal discomfort or a change in bowel habits may require stool studies, proctoscopic examination, or colonoscopy. Food intolerances, *C difficile* infection, and celiac disease should also be excluded.

The treatment of irritable bowel syndrome is reassurance, stress reduction, and a high-fiber diet or the use of fiber supplements. The use of antispasmodics to control abdominal pain or antimotility agents to control diarrhea should be reserved for patients who do not have response to a high-fiber diet.

Two therapies are FDA approved for diarrhea-predominant irritable bowel syndrome: rifaximin and eluxadoline. Rifaximin 550 mg twice daily for 14 days is more effective than placebo and most likely decreases diarrhea symptoms by reducing proximal intestinal bacterial overgrowth. If symptoms recur after treatment, subsequent courses can be given every 10 weeks.

More recently, eluxadoline 100 mg twice daily has been shown to be more effective than placebo for simultaneously decreasing abdominal pain and improving stool consistency over 26 weeks of treatment. This agent has agonist activity at the μ and κ opioid receptors and antagonist activity at the δ opioid receptor. Common adverse effects include constipation, nausea, abdominal pain, and, rarely, pancreatitis. Eluxadoline is contraindicated in those with a history of bile duct obstruction, pancreatitis, severe liver impairment, or severe constipation and in patients who drink more than 3 alcoholic beverages per day. The dose is decreased to 75 mg twice daily in those with prior cholecystectomy, and the drug should be discontinued if constipation is present lasting 4 days or longer.

KEY FACTS

✓ Vascular anatomy relevant for ischemia—

- celiac trunk: stomach and duodenum
- superior mesenteric artery: jejunum, ileum, and right side of the colon
- inferior mesenteric artery: left side of the colon and rectum

✓ Acute ischemia—

- symptoms: sudden and severe abdominal pain, vomiting, and diarrhea (with or without blood)
- early in course: severe abdominal pain but normal physical examination findings
- risk factors: severe atherosclerosis, congestive heart failure, atrial fibrillation, hypotension, and oral contraceptives

✓ Nonocclusive ischemia—due to poor tissue perfusion caused by inadequate cardiac output

✓ Symptoms of irritable bowel syndrome—

- usually of long duration
- usually associated with stressful situations
- usually no weight loss, no intestinal bleeding, and no associated organic symptoms (eg, arthritis or fever)

✓ Treatment of irritable bowel syndrome—

- reassurance, stress reduction, and a high-fiber diet (or fiber supplements)
- if patients have no response to high-fiber diet, use antispasmodics (for abdominal pain) and antimotility agents (for diarrhea)
- rifaximin or eluxadoline

Nontoxic Megacolon (Intestinal Pseudo-obstruction)

Acute pseudo-obstruction of the colon occurs postoperatively (after nonabdominal operations) and with spinal cord injury, sepsis, uremia, electrolyte imbalance, and use of certain drugs (narcotics, anticholinergics, and psychotropic agents). When the cecum diameter is more than 12 cm, the risk of perforation increases. Obstruction should be ruled out with a diatrizoate (Hypaque) enema. Treatment includes placement of a nasogastric tube, discontinuation of drug therapy, correction of metabolic abnormalities, and, if needed, neostigmine administration, colonoscopic decompression, or cecostomy.

Chronic pseudo-obstruction of the colon occurs with disorders that cause generalized intestinal pseudo-obstruction.

Congenital Megacolon

Congenital megacolon (Hirschsprung disease) occurs in 1 in 5,000 births. The incidence is increased with Down syndrome. Congenital megacolon usually becomes manifest in infancy; however, it can occur in adulthood. There is a variable length of aganglionic segment from the rectum to the proximal colon (usually confined to the rectum or rectosigmoid). The diagnosis is usually made at birth because of meconium ileus or obstipation. If the diagnosis is made when the patient is an adult, the patient usually has a history of chronic constipation. Radiography of the colon shows a characteristically narrowed distal segment and a dilated proximal colon. Rectal biopsy shows aganglionosis. Anorectal manometry shows loss of the anorectal inhibitory reflex. Treatment is with sphincter-saving operations.

Lower Gastrointestinal Tract Bleeding

Evaluation and Management

The evaluation of acute rectal bleeding should begin with a digital rectal examination, anoscopy, and proctosigmoidoscopy. If a definitive diagnosis cannot be made, colonoscopy is necessary. The inability to cleanse the colon appropriately during active bleeding can make colonoscopy difficult to perform and interpret. Some advocate the use of nuclear scanning if the extent of bleeding is uncertain. If clinically significant active bleeding cannot be treated endoscopically, angiography may be necessary. Colonoscopy is not useful if bleeding in the lower gastrointestinal tract is torrential, but it may be of some benefit with a slower rate of bleeding. Colonoscopy is valuable for evaluating patients who have unexplained rectal bleeding and persistently positive findings on tests for occult blood in the stool. Important causes of lower gastrointestinal tract bleeding are listed in Box 19.1.

In the evaluation of lower gastrointestinal tract bleeding, the patient's condition should be stabilized, proctoscopy performed to rule out rectal outlet bleeding (due to hemorrhoids or anal fissure), and a nasogastric tube aspirate obtained or esophagogastroduodenoscopy performed to rule out upper gastrointestinal tract bleeding. A radionuclide-tagged red blood cell scan may help determine whether bleeding is occurring, but it may not precisely localize the bleeding site. If bleeding stops or occurs at a slow rate, colonoscopy should be performed. If the patient is young, a Meckel scan should be performed. For persistent bleeding that is not amenable to endoscopic therapy, angiography may be used to localize the bleeding site; infusion of vasopressin or embolization may be useful. If colonoscopy shows bleeding, useful steps may include injection of epinephrine, electrocoagulation, or laser coagulation. If bleeding is massive or if marked bleeding continues, surgical management is necessary.

Box 19.1 • Important Causes of Lower Gastrointestinal Tract Bleeding

Angiodysplasia—usually involves the right side of the colon and small bowel; may respond to endoscopic treatment

Diverticular disease—usually bleeding without other symptoms

Inflammatory bowel disease (colitis)—in 5% of patients at presentation

Ischemic colitis—painful and bloody diarrhea

Cancer—rarely causes marked bleeding

Meckel diverticulum—the most common cause of lower gastrointestinal tract bleeding in young patients; it is usually painless

Internal hemorrhoids—painless with small volume of "outlet-type" bleeding

External hemorrhoids—pain with small volume of "outlet-type" bleeding

Anal fissure—painful defecation associated with small volume of "outlet-type" bleeding and often coexisting with constipation

Angiodysplasia

Angiodysplasia is a common cause of lower gastrointestinal tract bleeding in elderly patients. Usually involving the cecum and ascending colon, angiodysplasia is associated with cardiac disease (especially aortic stenosis), advanced age, and chronic renal insufficiency. There are no associated skin or visceral lesions. Radiography of the colon is of no diagnostic value, but angiography localizes the extent of involvement. Colonoscopy may show lesions, and cautery application may be effective.

Diverticular Disease of the Colon

Definitions

Diverticula are acquired herniations of the mucosa and submucosa through the muscular layers of the colonic wall. **Diverticulosis** is the mere presence of uninflamed diverticula of the colon. **Diverticulitis** is the inflammation of 1 or more diverticula. The diagnosis and management of the complications of diverticular disease are outlined in Table 19.2.

Key Definitions

***Diverticulosis:** presence of uninflamed diverticula of the colon.*

***Diverticulitis:** inflammation of 1 or more diverticula of the colon.*

Diverticulitis

Microperforation or macroperforation of the diverticulum with subsequent peridiverticular inflammation is necessary to produce diverticulitis. The severity of the clinical symptoms depends on the extent of inflammation. Free perforation is infrequent (diverticula are invested with longitudinal muscle and mesentery). Local perforations may dissect along the colonic wall and form intramural fistulas. The clinical presentation is left lower quadrant pain, fever, abdominal distention, change in bowel habits, and, occasionally, a palpable tender mass. Treatment includes resting the bowel or using a low-fiber diet and antibiotics and obtaining an early surgical consultation. Indications for surgical treatment include generalized peritonitis, an enlarging inflammatory mass, fistula formation, colonic obstruction, inability to rule out carcinoma in an area of stricture, or recurrent episodes of diverticulitis.

Colorectal Cancer Screening and Colonic Polyps

Screening Guidelines

Colorectal cancer is the second leading cause of cancer deaths in the United States in men and women combined. Screening for this disease by fecal occult blood testing and flexible sigmoidoscopy has been shown to decrease mortality rates. Large observational studies support the benefit of screening by colonoscopy. The US Preventive Services Task Force has endorsed colorectal cancer screening with various tests (Table 19.3). Screening for persons without a strong family history, inflammatory bowel disease, or genetic syndrome typically begins at age 50 years and continues through 75 years; screening after age 75 years may be considered in patients without significant comorbid conditions on an individualized basis. Patients with a family history of colorectal cancer in a first-degree relative younger than 60 years should be screened at age 40 years or at an age 10 years before diagnosis in the affected relative. The goal of screening is to detect curable-stage colorectal cancer or, ideally, premalignant polypoid or flat neoplasms.

Table 19.2 • Diagnosis and Management of Complications of Diverticular Disease

Complication	Signs and Symptoms	Findings	Treatment
Diverticulitis	Pain, fever, and constipation or diarrhea (or both)	Palpable, tender colon Leukocytosis	Liquid diet (with or without antibiotics) or elective surgery
Pericolic abscess	Pain Fever (with or without tenderness) or pus in stools	Tender mass and guarding Leukocytosis Soft tissue mass on abdominal radiography or ultrasonography	Nothing by mouth Intravenous fluids Antibiotics Early surgical treatment with colostomy
Fistula	Depends on site: dysuria, pneumaturia, fecal discharge on skin or vagina	Depends on site: abnormal findings on fistulogram and methylene blue dye injection	Antibiotics Clear liquids Colostomy Later, resection
Perforation	Sudden, severe pain Fever	Sepsis Leukocytosis Free air	Antibiotics Nothing by mouth Intravenous fluids Immediate surgical treatment
Liver abscess	Right upper quadrant pain Fever Weight loss	Tender liver, bowel, or mass Leukocytosis Increased serum alkaline phosphatase level Filling defect on lumbosacral scan	Antibiotics Surgical drainage Operation for bowel disease
Bleeding	Bright red or maroon blood or clots	Blood on rectal examination Abnormal findings on sigmoidoscopy, colonoscopy, angiography	Conservative therapy Blood transfusion if needed, with or without operation

Table 19.3 • Colorectal Cancer Screening Tests

Screening Method	Frequency
Stool-based	
Guaiac fecal occult blood	Annually
Fecal immunochemical	Annually
Stool DNA	Every 3 years
Direct visualization	
Colonoscopy	Every 10 years
Computed tomography colonography	Every 5 years
Flexible sigmoidoscopy	Every 5 years

Three types of epithelial polyps are benign: hyperplastic, hamartomatous, and inflammatory polyps. **Hyperplastic polyps** are metaplastic, completely differentiated glandular elements. **Hamartomatous polyps** are a mixture of normal tissues. **Inflammatory polyps** are an epithelial inflammatory reaction.

Key Definitions

Hyperplastic polyp: *metaplastic, completely differentiated glandular elements.*

Hamartomatous polyp: *mixture of normal tissues.*

Inflammatory polyp: *epithelial inflammatory reaction.*

The fourth type of epithelial polyp, *adenomatous polyps*, results from failed differentiation of glandular elements. Adenomatous polyps are premalignant. The types of adenomatous polyps are *tubular adenoma, mixed* (*tubulovillous*) *adenoma*, and *villous adenoma*. The risk of cancer with any adenomatous polyp depends on 3 features: size larger than 1 cm, the presence of villous elements, and the presence of high-grade dysplasia.

Another type of polyp with neoplastic potential is the sessile serrated polyp (SSP, previously *sessile serrated adenoma*). SSP lesions do not have adenomatous features and may or may not contain frankly dysplastic-appearing cells. However, SSPs are thought to be critical precursor lesions for as many as one-third of all colorectal cancers. These typically arise in the right side of the colon and are often endoscopically inconspicuous because of their flat morphology.

Patients found to have premalignant polyps require ongoing surveillance by colonoscopy (Table 19.3).

Hereditary Nonpolyposis Colorectal Cancer

Familial colorectal cancer accounts for only about 20% of incident disease. Hereditary nonpolyposis colorectal cancer (HNPCC, also known as Lynch syndrome) is the most common cause of inherited colorectal cancer and also increases the risk of endometrial, stomach, ovarian, pancreas, ureter, renal pelvis, and biliary tract cancers and glioblastoma. HNPCC is caused by mutations—and thus absent expression—of mismatch repair genes *MLH1, MSH2, MLH6*, or *PMS2*. HNPCC should be suspected in patients with a pedigree suggesting autosomal dominant inheritance of colorectal cancer or other HNPCC-associated neoplasms.

Families in which at least 3 relatives have history of HNPCC cancers involving 2 successive generations and at least 1 person younger than 50 years are said to meet Amsterdam criteria ("3-2-1 rule") for HNPCC. Primary tumor tissue from those with such a pedigree should be phenotyped for deficient expression of the mismatch repair genes with immunohistochemistry. If a mutation in these genes is confirmed by germline testing, HNPCC can be diagnosed. Because of suboptimal sensitivity and specificity of the pedigree-based criteria, universal testing of colorectal cancer tumors for mismatch repair deficiency with immunohistochemistry or with PCR for microsatellite instability is recommended to identify patients who should undergo germline testing for HNPCC. They may also require testing for sporadic *BRAF* mutations if MLH1 protein expression is missing and *MLH1* mutation cannot be confirmed. First-degree relatives of patients with HNPCC should be offered mutation testing and cancer surveillance; those with *BRAF* mutations should not.

Hereditary Polyposis Syndromes Associated With Risk of Cancer

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is characterized by adenomatous polyps of the colon. Colorectal carcinoma develops in more than 95% of patients, typically by age 40 years, if prophylactic colectomy is not performed. Diagnosis is suspected on the basis of family history and documentation of adenomatous polyps; germline *APC* gene mutation is confirmatory. Screening is indicated for all family members, and colectomy is indicated before cancer develops. The inheritance is autosomal dominant; however, the phenotypic expression may vary considerably. The second most common cancer in patients with FAP is duodenal; this typically presents in the 5th decade or after.

The Gardner syndrome variant of FAP includes additional, extraintestinal manifestations, including congenital hypertrophy of the retinal pigment epithelium; osteomas of the mandible, skull, and long bones; supernumerary teeth; soft tissue tumors; thyroid and adrenal tumors; and epidermoid and sebaceous cysts. Patients with 10 to 100 polyps should be offered *APC* mutation testing to exclude attenuated FAP.

MUTYH-Associated Polyposis

Mutations in the *MUTYH* gene cause an autosomal recessive attenuated polyposis phenotype. *MUTYH* is another gene involved in DNA repair, and decreased expression causes mutations in other tumor suppressor genes (eg, *APC*) and oncogenes (eg, *KRAS*). *MUTYH*-associated polyposis causes colorectal cancer in the 5th or 6th decade; associated cancers include those of the duodenum, ovaries, bladder, thyroid, and skin, and benign extraintestinal manifestations resemble those of Gardner syndrome.

Hamartomatous Polyposis Syndromes

Colorectal cancer risk is also markedly increased in patients who have hamartomatous polyposis of the gastrointestinal tract. In Peutz-Jeghers syndrome, hamartomas occur in the small intestine and, less commonly, in the stomach and colon. A hallmark extraintestinal finding is mucocutaneous pigmentation. Associated cancers involve the gastrointestinal tract lumen, pancreas, breast, gonads, cervix, and thyroid. Polyps may cause bleeding or intestinal obstruction and may involve the respiratory or urinary epithelia. The inheritance is autosomal dominant.

Juvenile polyposis syndrome polyps may also cause colorectal and gastric cancers. This disease is also associated with hereditary hemorrhagic telangiectasia because both are caused by autosomal dominant mutations in the *SMAD4* gene.

KEY FACTS

✓ Evaluation of acute rectal bleeding—
  - initially, digital rectal examination, anoscopy, and proctosigmoidoscopy
  - if definitive diagnosis is not possible, colonoscopy is necessary

✓ Angiodysplasia—common cause of lower gastrointestinal tract bleeding in elderly patients

✓ Clinical presentation of diverticulitis—left lower quadrant pain, fever, abdominal distention, change in bowel habits, and, occasionally, a palpable tender mass

✓ Familial adenomatous polyposis (FAP)—
  - adenomatous polyps of the colon
  - without prophylactic colectomy, 95% of patients have colorectal carcinoma (usually by age 40 years)

✓ Peutz-Jeghers syndrome—
  - hamartomas occur in small intestine (less commonly, in stomach and colon)
  - pigmented lesions of the mouth, hands, and feet (associated with ovarian sex cord tumors and proximal small bowel tumors)
  - autosomal dominant inheritance

20 Diarrhea, Malabsorption, and Small-Bowel Disorders

SETH R. SWEETSER, MD

Diarrhea

Definitions

***Diarrhea* is a** symptom or a sign, not a disease. As a symptom, it can manifest as 1 or more of the following: a decrease in consistency, an increase in fluidity, or an increase in number or volume of stools. A stool frequency of 3 or more times daily is considered abnormal; however, most people consider increased fluidity of stool as the essential characteristic of diarrhea. As a sign, diarrhea is an increase in stool weight or volume of more than 200 g or 200 mL per 24 hours for a person eating a Western diet. Although stool weight is often used in the objective definition, diarrhea should not be strictly defined by stool weight because the amount of dietary fiber influences the water content of the stool. Therefore, stool weight can vary considerably depending on fiber intake. In the United States, normal stool weight or volume is less than 200 g or 200 mL daily because of lower fiber intake (compared with up to 400 g or 400 mL daily in rural Africa).

Because diarrhea has multiple causes, its evaluation is often complex and time consuming. An understanding of the basic pathogenic mechanisms leading to diarrhea can help facilitate its evaluation and management.

The basic mechanism of all diarrheal diseases is incomplete absorption of fluid from luminal contents. Each day, approximately 10 L of fluid passes into the proximal small intestine (2 L from diet; 8 L from endogenous secretions). The small bowel absorbs most of the fluid (9 L), and the colon absorbs about 90% of the remaining 1 L, so that only about 1% of the original fluid entering the small intestine is excreted in the stool. A normal stool is approximately 75% water and 25% solids, with a normal fecal water output of 60 mL daily. An increase in fecal water output of only 100 mL is enough to cause increased stool fluidity or decreased stool consistency. This volume is approximately 1% of the fluid entering the proximal small intestine each day. Hence, malabsorption of only 1% of the fluid entering the intestine may be sufficient to cause diarrhea. Fortunately, the gut has considerable reserve absorptive capacity, with the small intestine having a maximal absorptive capacity of 12 L daily and the colon, 6 L daily.

Mechanisms of Diarrhea

Osmotic diarrhea occurs when a poorly absorbed substance remains in the intestinal lumen and causes water retention that maintains an intraluminal osmolality equal to that of body fluids (approximately 290 mOsm/kg). This occurs because, unlike the kidney, neither the small intestine nor the colon maintains an osmotic gradient. Osmotic diarrhea follows ingestion of an osmotically active substance and stops with fasting. Stool volume is less than 1 L daily, and the stool osmotic gap (SOG), calculated as follows, is greater than the sum of the measured concentrations of sodium (Na) and potassium (K) (the sum is doubled to account for their associated anions):

$$\text{SOG} = 290\,\text{mOsm/kg} - 2 \times (\text{Stool}[\text{Na}] + \text{Stool}[\text{K}]).$$

A normal SOG is less than 50 mOsm/kg. However, with an osmotically active substance in the bowel, sodium and potassium levels will decrease (keeping stool osmotically neutral with the body). The calculated stool osmolality decreases, resulting in a gap (typically >100 mOsm/kg). Clinical causes of osmotic diarrhea include carbohydrate malabsorption, lactase deficiency, sorbitol-sweetened foods, saline cathartics, and magnesium-based antacids. In carbohydrate malabsorption (most commonly lactase deficiency), stool pH is often less than 6.0 because of colonic fermentation of the undigested sugars.

The term **secretory diarrhea** is used to indicate disordered intestinal epithelial electrolyte transport (ie, the intestine secretes electrolytes and fluid rather than absorbing them) even though secretory diarrhea is more commonly caused by decreased absorption than by net secretion. Stool volume is more than 1 L daily. The stool composition is predominantly extracellular fluid, so there is no SOG. Secretory diarrhea persists despite fasting. Types of secretory diarrhea include bile acid diarrhea and fatty acid diarrhea, and causes include bacterial toxins, neuroendocrine tumors, and surreptitious ingestion of laxative.

Key Definition

Secretory diarrhea: *disordered intestinal electrolyte secretion and/or fluid absorption.*

A useful method to evaluate chronic watery diarrhea is to distinguish secretory diarrhea from osmotic diarrhea (Table 20.1) by measuring the concentrations of sodium and potassium in stool water (and calculating the SOG) and observing the patient's response to fasting.

Many disease processes cause diarrhea by more than 1 mechanism. For example, malabsorption in celiac disease has osmotic components (from carbohydrate malabsorption) and secretory components (from unabsorbed fatty acids causing secretion in the colon).

In **exudative diarrhea**, abnormal membrane permeability allows serum proteins, blood, or mucus to be exuded into the bowel from sites of inflammation, ulceration, or infiltration. The volume of feces is small and the stools may be bloody. Examples include invasive bacterial pathogens (eg, *Shigella* and *Salmonella*) and inflammatory bowel disease. In motility disorders, both *rapid transit* (inadequate time for chyme to contact the absorbing surface) and *delayed transit* (bacterial overgrowth) can cause diarrhea. Rapid transit occurs after gastrectomy or intestinal resection and with hyperthyroidism or carcinoid syndrome. Delayed transit occurs with structural defects (strictures, blind loops, and small-bowel diverticula) or with underlying illnesses that cause visceral neuropathy (diabetes mellitus) or myopathy (scleroderma), which result in pseudo-obstruction.

Table 20.1 • Features That Distinguish Osmotic Diarrhea From Secretory Diarrhea

Feature	Osmotic Diarrhea	Secretory Diarrhea
Daily stool volume, L	<1	>1
Effect of 48-h fasting	Diarrhea stops	Diarrhea continues
Fecal fluid analysis		
Osmolality, mOsm	290	290
([Na] + [K]) × 2[a], mEq/L	120	280
Stool osmotic gap[b]	>100	<50

Abbreviations: K, potassium; Na, sodium.

[a] Multiplied by 2 to account for anions.

[b] Calculated by subtracting ([Na] + [K]) × 2 from osmolality.

Modified from Krejs GJ, Hendler RS, Fordtran JS. Diagnostic and pathophysiologic studies in patients with chronic diarrhea. In: Field M, Fordtran JS, Schultz SG, editors. Secretory diarrhea. Bethesda (MD): American Physiological Society; c1980. p. 141-51; used with permission.

KEY FACTS

- ✓ Basic mechanism of diarrhea—incomplete absorption of fluid
- ✓ Osmotic diarrhea resolves with fasting; secretory diarrhea does not
- ✓ Causes of osmotic diarrhea—carbohydrate malabsorption, lactase deficiency, sorbitol, saline cathartics, and magnesium-based antacids

Key Definition

Exudative diarrhea: *serum proteins, blood, or mucus are exuded into the bowel from sites of inflammation, ulceration, or infiltration.*

Clinical Approach to Diarrhea

Knowing the stool volume is potentially useful for distinguishing between diarrhea arising from the small bowel or ascending colon ("right-sided diarrhea") and diarrhea arising from the distal colon ("left-sided diarrhea") (Table 20.2). The distal colon acts as a distensible reservoir that collects stool until defecation. With inflammation of the distal colon, the reservoir becomes spastic, and its ability to accommodate normal volumes of stool is impaired. As a result, left-sided diarrhea is characterized by frequent, small-volume stools and tenesmus with evidence of inflammation (blood or pus) in the stools. Proctosigmoidoscopic examination usually confirms mucosal inflammation.

Right-sided diarrhea is characterized by large-volume stools (due to normal distensibility of the rectum) and a modest increase in the number of stools. Symptoms attributed to inflammation of the rectosigmoid are absent, and proctoscopic examination findings are normal. Left-sided diarrhea usually suggests an exudative mechanism, whereas the mechanism for right-sided diarrhea is nonspecific.

Acute Diarrhea

Acute diarrhea is abrupt in onset and usually resolves in 3 to 10 days. It is self-limited, and the cause (often viral)

Table 20.2 • Features That Distinguish Right-Sided Diarrhea From Left-Sided Diarrhea

Feature	Right-Sided (Small-Bowel) Diarrhea	Left-Sided (Colonic) Diarrhea
Reservoir capacity	Intact	Decreased
Stool volume	Large	Small
Increase in number of stools	Modest	Large
Urgency	Absent	Present
Tenesmus	Absent	Present
Mucus	Absent	Present
Blood	Absent	Present

usually is not found. No evaluation is necessary unless an invasive infection is suspected (eg, on the basis of bloody stools, fever, travel history, immunocompromise, or a common source outbreak). If these conditions exist, antimotility agents should not be used for treatment. The evaluation should begin with stool studies for bacterial pathogens, ova, and parasites and proctosigmoidoscopy. The clinician should recognize the common situations that cause predisposition to specific infections (see Noninvasive [Toxicogenic] Bacterial Diarrhea subsection).

Chronic Diarrhea

Chronic diarrhea is defined as diarrhea lasting longer than 4 weeks. The most common cause of chronic diarrhea is irritable bowel syndrome, but lactase deficiency should always be considered. Several features help distinguish organic diarrhea from functional diarrhea (Table 20.3).

Key Definitions

Acute diarrhea: *duration of 3-10 days after abrupt onset.*

Chronic diarrhea: *duration of >4 weeks.*

Physiology of Nutrient Absorption

The sites of nutrient, vitamin, and mineral absorption are depicted in Figure 20.1. The proximal small bowel absorbs iron, calcium, fat, sugars, folate, water-soluble vitamins, and amino acids. The middle small bowel absorbs sugars, fatty acids, water-soluble vitamins, and amino acids. The distal small bowel absorbs bile salts, sugars, fat-soluble vitamins (A, D, E, and K), and vitamin B_{12}.

Table 20.3 • Features That Distinguish Organic Diarrhea From Functional Diarrhea

Feature	Organic Diarrhea	Functional Diarrhea
Weight loss	Often present	Absent
Duration of illness	Variable (weeks to years)	Usually long (>6 months)
Quantity of stool	Variable but usually large (>200 g in 24 hours)	Usually small (<200 g in 24 hours)
Blood in stool	May be present	Absent (unless from hemorrhoids)
Timing of diarrhea	No special pattern	Usually in the morning or after meals
Nocturnal symptoms	May be present	Absent
Fever, arthritis, skin lesions	May be present	Absent
Emotional stress	No relation to symptoms	Usually precedes or coincides with symptoms
Cramping abdominal pain	Often present	May be present

Modified from Matseshe JW, Phillips SF. Chronic diarrhea: a practical approach. Med Clin North Am. 1978 Jan;62(1):141-54; used with permission.

Fat is the most complex macronutrient to absorb. Dietary fat consists mostly of long-chain triglycerides that must be digested by pancreatic lipase, which cleaves 2 of the 3 long-chain fatty acids from the glycerol backbone. The resultant free fatty acids and monoglycerides are solubilized by micelles for absorption. The fatty acids and monoglycerides are reesterified by intestinal epithelial cells into chylomicrons that are absorbed into the circulation via lymphatic vessels. Conversely, medium-chain triglycerides are absorbed directly into the portal venous system and do not require micellar solubilization.

Mechanisms of fat malabsorption are summarized in Table 20.4. Malabsorption should be suspected if the medical history suggests steatorrhea or if diarrhea occurs with weight loss (especially if intake is adequate), chronic diarrhea of indeterminate nature, or nutritional deficiency.

The causes of symptoms in malabsorption are summarized in Table 20.5, and various features that suggest specific malabsorption conditions are listed in Table 20.6.

The medical history, physical examination, or laboratory results may suggest a possible cause of diarrhea or malabsorption (Tables 20.7 and 20.8). For example, the medical history may include previous surgery (resulting in short bowel syndrome [SBS], dumping syndrome, blind loop syndrome, postvagotomy diarrhea, or ileal resection), irradiation, or systemic disease.

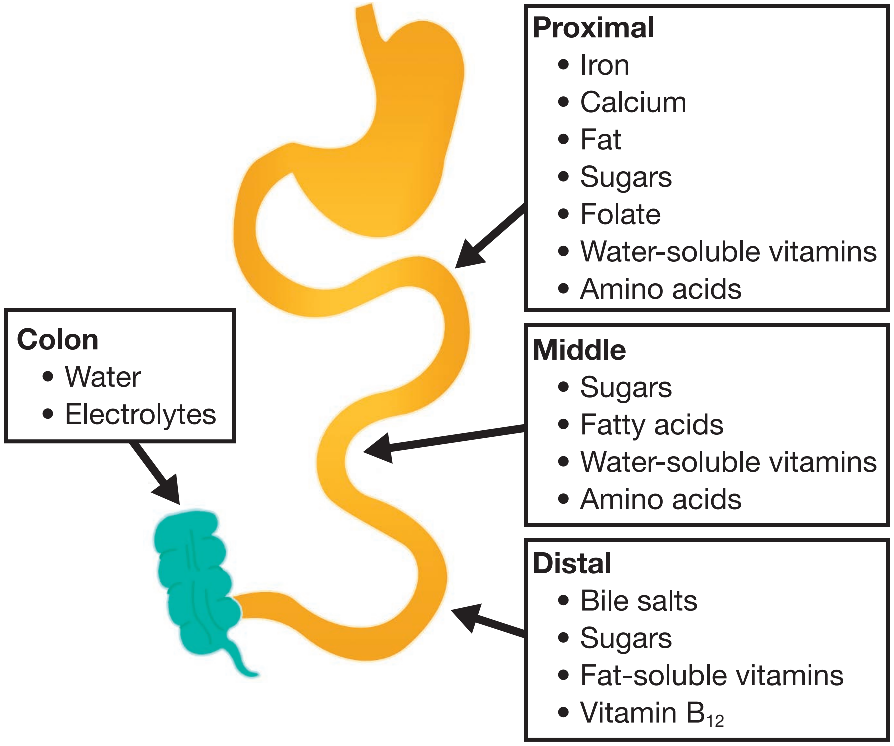

Figure 20.1. *Sites of Nutrient Absorption.*

Diseases Causing Diarrhea

Osmotic Diarrhea

Lactose is normally split by the brush border enzyme lactase into glucose and galactose, which are absorbed in the small bowel. In lactase deficiency, lactose is not split in the small intestine but enters the colon, where it is fermented in the lumen by bacteria, forming lactic acid and liberating hydrogen. The result is diarrhea of low pH and increased intestinal motility. Several other disaccharidase deficiencies can also result in malabsorption of specific carbohydrates; however, the most common disaccharidase deficiency involves lactase.

"Acquired" lactase deficiency (which is possibly genetic) is common in African Americans, Native Americans, and peoples of Asia and the Middle East. Diarrhea, abdominal cramps, and flatulence occur after ingestion of dairy products. The diarrhea improves with dietary changes. The pH of the stool is less than 6.0. In the lactose tolerance test, blood glucose levels increase less than 20 mg/dL after ingestion of lactose. Results of the hydrogen breath test may be abnormal. Jejunal biopsy results are normal (disaccharidase levels are decreased).

Transient lactose intolerance can occur whenever the intestinal mucosa is damaged, including by simple viral gastroenteritis. In patients who eat a weight-reduction diet and drink diet soda or chew sugarless gum, osmotic diarrhea may develop from excessive ingestion of fructose or artificial sweeteners.

Table 20.4 • Mechanisms of Fat Malabsorption

Alteration	Mechanism	Disease State
Defective digestion	Inadequate lipase	Pancreatic insufficiency
Impaired micelle formation	Duodenal bile salt concentration	Common bile duct obstruction or cholestasis
Impaired absorption	Small-bowel disease	Celiac disease, Whipple disease
Impaired chylomicron formation	Impaired β-globulin synthesis	Abetalipoproteinemia
Impaired lymphatic circulation	Lymphatic obstruction	Intestinal lymphangiectasia, intestinal lymphoma

Table 20.5 • Causes of Symptoms in Malabsorption

Extragastrointestinal Symptom	Cause
Muscle wasting, edema	Decreased protein absorption
Paresthesias, tetany	Decreased vitamin D and calcium absorption
Bone pain	Decreased calcium absorption
Muscle cramps	Weakness, excess potassium loss
Easy bruisability, petechiae	Decreased vitamin K absorption
Hyperkeratosis, night blindness	Decreased vitamin A absorption
Pallor	Decreased vitamin B_{12}, folate, or iron absorption
Glossitis, stomatitis, cheilosis	Decreased vitamin B_{12} or iron absorption
Acrodermatitis	Zinc deficiency

KEY FACTS

- ✓ Acute diarrhea—self-limited; treatment is supportive
- ✓ Chronic diarrhea—broad differential diagnosis
- ✓ Malabsorption—suspect with steatorrhea, diarrhea with weight loss, chronic diarrhea of indeterminate nature, or nutritional deficiency
- ✓ Any damage to the intestinal mucosa (eg, simple viral gastroenteritis) can cause transient lactose intolerance

Table 20.6 • Features That Suggest Malabsorption Conditions

Feature	Condition
Diarrhea with iron deficiency anemia (evaluation for blood loss is negative)	Proximal small-bowel malabsorption (eg, celiac disease)
Diarrhea with metabolic bone disease	Proximal small-bowel malabsorption (from decreased calcium and protein levels)
Hypoproteinemia with normal fat absorption	Protein-losing enteropathy (with eosinophilia, eosinophilic gastroenteritis; with lymphopenia, intestinal lymphangiectasia)
Oil droplets (neutral fat) or muscle fibers (undigested protein) present in stool	Pancreatic insufficiency (maldigestion)
Normal serum levels (usually) of calcium, magnesium, and iron	Pancreatic insufficiency (serum levels of albumin may also be normal)
Howell-Jolly bodies (if there is no history of splenectomy) or dermatitis herpetiformis	Celiac disease
Fever, arthralgia, and neurologic symptoms	Whipple disease

Table 20.7 • Patient History Features That May Suggest a Possible Cause of Diarrhea or Malabsorption

Feature	Suggested Cause
Age	Youth: lactase deficiency, inflammatory bowel disease, or celiac disease
Travel	Parasites or toxicogenic agents (exposure to contaminated food or water)
Drugs	Laxatives, antacids, antibiotics, colchicine, or lactulose
Family history	Celiac disease, inflammatory bowel disease, polyposis coli, or lactase deficiency

Secretory Diarrhea

VIPoma

The **WDHA syndrome** (watery diarrhea, hypokalemia, and achlorhydria), also called Verner-Morrison syndrome or pancreatic cholera, is a massive diarrhea (5 L daily) with dehydration and hypokalemia. The patient may have numerous endocrine tumors (with hypercalcemia or hyperglycemia). This diarrhea is associated with a non–beta islet cell tumor of the pancreas. Vasoactive intestinal polypeptide, VIP, is the most common mediator; other mediators are prostaglandin, secretin, and calcitonin. VIPoma is diagnosed with a pancreatic scan or angiography and measurement of hormone levels. Treatment is with somatostatin or surgery.

Table 20.8 • Associated Signs and Symptoms of Systemic Illnesses Causing Diarrhea

Sign or Symptom	Diagnosis to be Considered
Arthritis	Ulcerative colitis, Crohn disease, Whipple disease, *Yersinia* infection
Marked weight loss	Malabsorption, inflammatory bowel disease, cancer, thyrotoxicosis
Eosinophilia	Eosinophilic gastroenteritis, parasitic disease
Lymphadenopathy	Lymphoma, Whipple disease
Neuropathy	Diabetic diarrhea, amyloidosis
Postural hypotension	Diabetic diarrhea, Addison disease, idiopathic orthostatic hypotension, autonomic dysfunction
Flushing	Malignant carcinoid syndrome
Proteinuria	Amyloidosis
Peptic ulcers	Zollinger-Ellison syndrome
Skin hyperpigmentation	Whipple disease, Addison disease

Modified from Fine KD. Diarrhea. In: Feldman M, Scharschmidt BF, Sleisenger MH, editors. Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology, diagnosis, management. 6th ed. Vol. 1. Philadelphia (PA): WB Saunders Company; c1998. p. 128-52; used with permission.

Key Definition

WDHA syndrome: *watery diarrhea, hypokalemia, and achlorhydria.*

Carcinoid Syndrome

Carcinoid tumors arise from enterochromaffin cells of neural crest origin, with the most common location being the small intestine. About 90% of tumors are in the terminal ileum. Features of carcinoid syndrome include episodic facial flushing (lasting up to 10 minutes), watery diarrhea, wheezing, right-sided valvular disease (endocardial fibrosis), and hepatomegaly. Carcinoid syndrome only occurs with liver metastasis of gastrointestinal carcinoid tumors. Extraintestinal locations of carcinoid tumors include the bronchus and gonads. Dietary tryptophan is converted into serotonin (which causes diarrhea, abdominal cramps [intestinal hypermotility], nausea, and vomiting), histamine (responsible for flushing), and other chemicals (bradykinin and corticotropin). Persons with intestinal tumors are usually asymptomatic initially because the mediators have high first-pass clearance in the liver. Carcinoid syndrome arises when these mediators are released into the systemic bloodstream; this suggests that liver metastases or bronchial tumors are present. The diagnosis of carcinoid syndrome is made by finding increased urinary levels of 5-hydroxyindoleacetic acid and by performing liver biopsy. Treatment is with octreotide.

Laxative Abuse and Surreptitious Laxative Ingestion

Of the population older than 60 years, 15% to 30% admit that they take laxatives regularly. With the concealed ingestion of laxatives (surreptitious laxative ingestion), patients report diarrhea but do not admit to their providers that they take laxatives. In referral centers, this is a common cause of chronic watery diarrhea. Colonoscopy may show melanosis coli, which is a brown discoloration of the mucosa due to lipofuscin pigment accumulating in lamina propria macrophages. Melanosis coli is caused by anthraquinone laxatives (senna, cascara, and aloe). This benign condition is reversible with discontinuation of laxative use. A high degree of awareness is required to detect this condition. When surreptitious laxative ingestion is suspected, stool water can be analyzed for laxatives by chemical or chromatographic methods. Patients who ingest laxatives surreptitiously often have underlying emotional problems that should be addressed.

Bile Acid Malabsorption

Bile acid malabsorption is caused by ileal resection or disease. Diarrhea due to bile acid malabsorption may produce 2 clinical syndromes, each requiring a different treatment.

With a *limited resection* (≤100 cm of small intestine), malabsorbed bile acids enter the colon and stimulate secretion. Liver synthesis can compensate, so bile acid concentration in the upper small bowel is sufficient to achieve the critical micelle concentration and allow for normal fat absorption. The excess bile acids irritate the colon mucosa, which causes a secretory diarrhea with minimal fat malabsorption. Treatment of the diarrhea is with cholestyramine, which binds excess bile acids.

With an *extensive resection* (>100 cm of small intestine), bile acid malabsorption is severe and enterohepatic circulation is interrupted. This limits bile acid reabsorption, and the liver cannot compensate for large bile acid losses. Bile acid concentration is decreased in the upper small bowel, micelles cannot be formed, and fat malabsorption results. The malabsorbed fatty acids themselves stimulate secretion in the colon. Fat-soluble vitamins (A, D, E, and K) may be malabsorbed. Additionally, excess fatty acids bind intestinal calcium; this allows for an increase in oxylate absorption, which increases the risk of oxylate renal stones. The treatment of this bile acid malabsorption is a low-fat diet (<50 g daily) rich in medium-chain triglycerides. Cholestyramine would further decrease the bile acid concentration and worsen the steatorrhea.

Short Bowel Syndrome

SBS occurs after resection of a large proportion of the small intestine and colon, with substantial loss of absorptive area. The remaining absorptive surface is insufficient to preserve nutrient, fluid, and/or electrolyte balance. SBS is not likely to develop if more than 200 cm of the small intestine remains. However, the risk of SBS also relates to which part of the small bowel is resected, the functional integrity of the remaining intestine, and whether it is in continuity with the colon.

The most common causes of SBS are extensive bowel resections secondary to Crohn disease, mesenteric vascular ischemia, or tumors. Symptoms depend on the length and location of the remaining bowel. Patients may initially require intravenous fluids and total parenteral nutrition (TPN). Over time, bowel adaptation can occur, with intestinal elongation, dilatation, and increased absorptive capacity.

Treatment of SBS is directed at limiting dependence on TPN. Oral rehydration solution, small frequent meals, and antimotility agents are used. Disease severity can change over time because of intestinal adaptation. Patients with more than 100 cm of small bowel in continuity with the colon are not normally TPN dependent. Conversely, patients with less than 100 cm of small bowel and/or loss of colon are usually TPN dependent. Prolonged TPN can result in liver injury and vascular access problems. A small bowel transplant is an option for select patients but is associated with an increased mortality rate.

KEY FACTS

- ✓ Diagnosis of carcinoid syndrome—based on liver biopsy findings and increased urinary levels of 5-hydroxyindoleacetic acid
- ✓ Causes of bile acid malabsorption—ileal resection or disease
- ✓ Limited resection of small intestine (≤100 cm)—malabsorbed bile acids enter the colon, stimulating secretion
- ✓ Extensive resection of small intestine (>100 cm)—severe bile acid malabsorption and interrupted enterohepatic circulation

Bacterial Overgrowth

The proximal small intestine normally has low bacterial counts because it has several major defenses against excess small intestinal bacterial proliferation: intestinal peristalsis (the most important defense), gastric acid, and intestinal immunoglobulin (Ig) A. When these defenses are altered, bacterial overgrowth results. The mechanism of steatorrhea in bacterial overgrowth is the deconjugation of bile acids by bacteria that normally do not occur in the proximal intestine. Deconjugation of bile acids changes the ionization coefficient, and the deconjugated bile acids can then be passively absorbed in the proximal small bowel. Normally, conjugated bile acids are actively absorbed distally in the ileum. As a result, the critical micellar concentration is not reached, and mild steatorrhea results from the intraluminal deficiency of bile acids.

Clinical features of bacterial overgrowth are steatorrhea (typically >20 g daily), vitamin B_{12} malabsorption (macrocytic anemia), increased serum folate levels from bacterial production, and positive duodenal or jejunal cultures. Conditions associated with small-intestinal bacterial overgrowth include postoperative conditions (blind loops, enteroenterostomy, or gastrojejunocolic fistula); structural abnormalities (diverticula, strictures, or fistulas); motility disorders (diabetes mellitus, scleroderma, or pseudo-obstruction); achlorhydria (atrophic gastritis or gastric resections; achlorhydria is corrected with antibiotics); and impaired immunity. Two examples of impaired immunity are hypogammaglobulinemic sprue (in small-bowel biopsy specimens, no plasma cells are seen in the lamina propria and the villi are flat) and nodular lymphoid hyperplasia associated with IgA deficiency, which predisposes to *Giardia lamblia* infection.

Noninvasive (Toxicogenic) Bacterial Diarrhea

Toxicogenic bacterial diarrhea, characterized by watery stools without fecal leukocytes, is caused by several organisms (Table 20.9).

Table 20.9 • Toxicogenic Causes of Bacterial Diarrhea

Organism	Onset, h	Mediated by Cyclic AMP	Fever	Intestinal Secretion
Staphylococcus aureus	1-6	+	–	+
Clostridium perfringens	8-12	–	±	+
Escherichia coli	12	+	+	+
Vibrio cholerae	12	+	–	++++
Bacillus cereus	1-6	+	–	+

Abbreviations: –, absence of feature; +, presence of feature (++++, strong presence); ±, feature may be present or absent; AMP, adenosine monophosphate.

Staphylococcus aureus

Diarrhea caused by *S aureus* is of rapid onset and lasts for 24 hours. It is not accompanied by fever, vomiting, or cramps. The toxin is ingested with egg products, cream, and mayonnaise. Treatment is supportive.

Clostridium perfringens

The toxin of *C perfringens* (the “buffet pathogen”) is ingested with precooked foods, usually beef and turkey, which have been kept warm under heating lamps in buffet lines. Heat-stable spores produce toxins. Although the bacteria are killed and the toxin is destroyed, the spores survive. When food is rewarmed, the spores germinate and produce toxin. The diarrhea is worse than the vomiting and is later in onset. It lasts 24 hours. Treatment is supportive.

Escherichia coli

The toxin of *E coli*, which causes traveler’s diarrhea, is ingested with water and salads. It is a plasmid-mediated enterotoxin. Treatment is rehydration with correction of electrolyte imbalance and administration of ciprofloxacin, norfloxacin, or trimethoprim-sulfamethoxazole. This pathogen may be important in epidemic diarrhea of newborns.

Vibrio cholerae

The toxin of *V cholerae* is ingested with water. It is one of the few toxicogenic bacterial diarrhea illnesses in which antibiotics shorten the duration of the disease. Treatment is with tetracycline.

Bacillus cereus

Classically, the source of the *B cereus* toxin is fried rice in Asian restaurants. The toxin produces 2 syndromes: a rapid-onset syndrome that resembles *S aureus* infection and a slower-onset syndrome that resembles *C perfringens* infection. The diagnosis is typically made by clinical history but occasionally by isolating the organism from contaminated food. Treatment is supportive.

Other Toxicogenic Bacteria

Clostridium botulinum produces a neurotoxin that is ingested in improperly home-processed vegetables, fruits, and meats. It interferes with the release of acetylcholine from peripheral nerve endings. *Clostridioides difficile* (formerly known as *Clostridium difficile*) is discussed in the “Antibiotic Colitis” subsection of Chapter 19 (“Colonic Disorders”).

Invasive Bacterial Diarrhea

Invasive bacterial diarrhea is characterized by fever, bloody stools, and fecal leukocytes. It is caused by several organisms (Table 20.10).

Table 20.10 • Causes of Invasive Bacterial Diarrhea

Organism	Fever	Bloody Diarrhea	Bacteremia	Antibiotic Effectiveness
Shigella	+	+	+	+
Salmonella	+	−	−	−
Vibrio parahaemolyticus	+	+	−	+[a]
Escherichia coli	+	+	−	−
Staphylococcus aureus (enterocolitis)	+	+	±	+
Yersinia enterocolitica	+	+	+	+
Campylobacter jejuni	+	+	±	+
Vibrio vulnificus	+	+	+	+

Abbreviations: −, absence of feature; +, presence of feature; ±, feature may be present or absent.

[a] Antibiotics are of questionable value, but erythromycin may be most effective.

Shigella

Shigella infection is often acquired outside the United States. Bloody diarrhea is characteristic, and fever and bacteremia occur. Diagnosis is based on positive stool and blood cultures. Treatment is with ampicillin or a fluoroquinolone. Resistant strains are emerging for which chloramphenicol is an alternative.

Salmonella (Non-Typhi)

In the United States, *Salmonella typhimurium* is the most common agent. The organism is ingested with poultry. Fever and bloody diarrhea may be present. Diagnosis is based on a stool culture positive for *Salmonella*. Treatment is supportive. Severe symptoms should be treated with ciprofloxacin. Treating mild symptoms with other antibiotics may result in a prolonged carrier state.

Vibrio parahaemolyticus

The *V parahaemolyticus* toxin is ingested with undercooked shellfish. The infection is increasing in frequency in the United States (it is common in Japan). Fever and bloody diarrhea are the chief characteristics. Diagnosis is based on a stool culture positive for *Vibrio*. Antibiotics are of questionable value in treating this infection, but erythromycin may be most effective.

Escherichia coli

In the United States, enteroinvasive *E coli* is a rare cause of diarrhea. Enteroinvasive *E coli* affects the colon and causes abdominal pain with fever, bloody diarrhea, and profound toxicity (similar to *Shigella* infection). Shiga toxin–producing (also called enterohemorrhagic) *E coli* (serotype O157:H7) produces a cytotoxin that damages vascular endothelial cells. This serotype can cause sporadic or epidemic illness from contaminated ground beef and raw milk. Enterohemorrhagic *E coli* infection should be suspected when bloody diarrhea occurs after eating ground beef and when bloody diarrhea is complicated by hemolytic uremic syndrome or thrombotic thrombocytopenic purpura. Antibiotic treatment has not been effective and is not recommended because it may increase the risk of hemolytic uremic syndrome or thrombotic thrombocytopenic purpura from the rapid release of toxin during bacterial death.

Yersinia enterocolitica

A gram-negative rod, *Y enterocolitica* is hardy and can survive in cold temperatures. It grows on special cold-enriched medium. It is an invasive pathogen, with fecal-oral transmission in water and milk.

The spectrum of disease caused by *Y enterocolitica* includes acute and chronic enteritis. Acute enteritis is similar to shigellosis and usually lasts 1 to 3 weeks. It is characterized by fever, diarrhea, leukocytosis, and fecal leukocytes. Chronic enteritis occurs especially in children with diarrhea, failure to thrive, hypoalbuminemia, and hypokalemia. Other features are acute abdominal pain (mesenteric adenitis), nausea, and vomiting. The disease mimics appendicitis or Crohn disease.

Treatment is with aminoglycosides or trimethoprim-sulfamethoxazole. The bacteria are variably sensitive to tetracycline and chloramphenicol. β-Lactamases are frequently produced, which makes penicillin resistance common.

Campylobacter jejuni

The comma-shaped *C jejuni* organisms are motile, microaerophilic gram-negative bacilli. Transmission is linked to infected water, unpasteurized milk, poultry, sick dogs, and infected children. The incubation period is 2 to 4 days before invasion of the small bowel or colon. Infection results in the presence of blood and leukocytes in the stool. It may mimic granulomatous or idiopathic ulcerative colitis. The diarrhea usually lasts 3 to 5 days but may recur. Antibiotic treatment is with a macrolide antibiotic when symptoms are severe, but treatment often is not needed. Postdiarrheal illnesses are hemolytic uremic syndrome and postinfectious arthritis.

Vibrio vulnificus

Noncholera *V vulnificus* organisms are extremely invasive and produce necrotizing vasculitis, gangrene, and shock. They are routinely isolated from seawater, zooplankton, and shellfish along the Gulf of Mexico and both coasts of the United States, especially in the summer. The 2 clinical syndromes are 1) wound infection, cellulitis, fasciitis, or myositis after exposure to seawater or cleaning shellfish and 2) septicemia after the ingestion of raw shellfish (oysters). Patients at high risk for septicemia include those with liver disease, congestive heart failure, diabetes mellitus, renal failure, an immunosuppressive state, or hemochromatosis. Treatment is with tetracycline.

Aeromonas hydrophila

Infection with *A hydrophila* is a frequent cause of diarrhea after a person has been swimming in fresh or brackish water.

The organisms produce several toxins. Treatment is with trimethoprim-sulfamethoxazole and tetracycline.

KEY FACTS

- ✓ Bacterial overgrowth features—steatorrhea, vitamin B_{12} malabsorption, increased serum folate levels, and positive duodenal or jejunal cultures
- ✓ Noninvasive (toxicogenic) bacterial diarrhea—watery stools without fecal leukocytes
- ✓ Invasive bacterial diarrhea—fever and bloody stools with fecal leukocytes
- ✓ Treatment of non-Typhi *Salmonella* diarrhea—supportive; for severe symptoms, ciprofloxacin (use of other antibiotics for mild symptoms may lead to carrier state)
- ✓ Treatment of enterohemorrhagic *E coli* diarrhea—antibiotics are not effective and may increase the risk of hemolytic uremic syndrome or thrombotic thrombocytopenic purpura (from rapid release of toxin as bacteria die)

Malabsorption Due to Diseases of the Small Intestine

Celiac Disease

Celiac disease, also known as gluten-sensitive enteropathy, is a multisystem disorder affecting approximately 1% of the population. It may affect multiple organ systems and may have protean manifestations. Iron deficiency anemia is the most common clinical manifestation of celiac disease in adults. Gastrointestinal tract symptoms such as diarrhea are present in only approximately 50% of patients. Splenic atrophy may be a complication and cause abnormal peripheral blood smear findings with Howell-Jolly bodies, which may be a clue to the diagnosis in 10% to 15% of patients. The pathognomonic skin manifestation is dermatitis herpetiformis.

The measurement of serum IgA tissue transglutaminase antibodies is the test of choice for noninvasive screening. If the results are positive, a small-bowel biopsy should be performed. False-negative results can occur in the IgA-based tests because about 5% of patients with celiac disease also have IgA deficiency. IgG-based testing or confirmation of normal total IgA levels should be performed with all screening for celiac disease. If the result of the antibody testing is negative, another diagnosis should be considered. Small-bowel biopsy findings are not diagnostic. Diagnosis requires response to a gluten-free diet. If the patient has no response to the diet, the diet should be reviewed for inadvertent gluten ingestion. If symptoms recur after 10 to 15 years of successful dietary management, enteropathy-associated T-cell lymphoma—a characteristic complication of celiac disease—should be suspected, especially in the presence of associated abdominal pain and weight loss.

Tropical Sprue

In tropical sprue, diarrhea occurs 2 to 3 months after travel to the tropics. After 6 months, megaloblastic anemia develops because of folate deficiency and possible coexisting vitamin B_{12} deficiency. The pathogenesis is presumed to result from a type of bacterial overgrowth in the small bowel; however, the specific organism is somewhat controversial. Biopsies of the small bowel show villous atrophy, crypt hyperplasia, and an inflammatory infiltrate similar to findings in celiac disease. Treatment is with tetracycline (250 mg 4 times daily) and folate with or without vitamin B_{12}.

Whipple Disease

Whipple disease is a rare multisystem infectious disease that can involve the central nervous system (CNS), heart, kidneys, and small bowel. It occurs predominantly in middle-aged white men and is caused by chronic infection with the gram-positive bacillus *Tropheryma whipplei*. Diarrhea or steatorrhea is the most common presenting symptom. Arthritis is the most common extraintestinal symptom and affects most patients. When Whipple disease involves the CNS, it causes oculomasticatory myorhythmia in 20% of patients. Oculomasticatory myorhythmia is pathognomonic and is characterized by continuous rhythmic jaw contractions that are synchronous with dissociated pendular vergence oscillations of the eyes.

In most patients with Whipple disease, the intestinal tract is involved regardless of the presence or absence of gastrointestinal tract symptoms. Thus, the primary diagnostic approach to clinically suspected Whipple disease is upper endoscopy with mucosal biopsy. Intestinal biopsy specimens show the characteristic finding of macrophages with periodic acid-Schiff–staining particles that are *T whipplei* bacilli. Polymerase chain reaction may assist in detecting *T whipplei* DNA in the intestinal mucosa. Whipple disease should be suspected in patients who have recurrent arthritis, hyperpigmentation of the skin, adenopathy, or CNS symptoms (dementia, myoclonus, ophthalmoplegia, visual disturbances, coma, or seizures). Treatment is with trimethoprim-sulfamethoxazole for 1 year.

Eosinophilic Gastroenteritis

Patients with eosinophilic gastroenteritis have a history of allergies (eg, asthma), food intolerances, and episodic symptoms of nausea, vomiting, abdominal pain, and diarrhea. Laboratory findings include peripheral eosinophilia, iron deficiency anemia, and steatorrhea or protein-losing enteropathy. Small-bowel radiographs show coarse folds and filling defects, and biopsy specimens show infiltration of the mucosa by eosinophils and, occasionally, the absence of villi. Parasitic infection should be ruled out. Treatment with corticosteroids produces a rapid response.

Systemic Mastocytosis

Systemic mastocytosis is a clonal proliferation of mast cells with activating mutations in the *c-kit* gene. It is characterized by mast cell infiltration of tissues, including those in the bone marrow, spleen, liver, and gastrointestinal tract. The characteristic dermatologic finding is urticaria pigmentosa. Typical symptoms include pruritus, flushing, tachycardia, asthma, and headache caused by the release of histamine from mast cells. Gastrointestinal tract manifestations include diarrhea and peptic ulcer disease. Symptoms may be provoked by heat; hence, bath pruritus (ie, itching after a hot bath) is a clue to the diagnosis. Treatment includes histamine receptor blockers, anticholinergics, cromoglycate, and glucocorticoids. Although the *c-kit* gene is mutated, the tyrosine kinase inhibitor imatinib mesylate is not an effective treatment.

Intestinal Lymphangiectasia

Intestinal lymphangiectasia is caused by lymphatic obstruction that results in dilatation of intestinal lymphatic channels, with subsequent lacteal rupture and leakage of chylomicrons and protein-rich fluid into the intestine. The clinical features are edema (often unilateral leg edema), chylous peritoneal or pleural effusions, and steatorrhea or protein-losing enteropathy.

Laboratory findings include lymphocytopenia (average lymphocyte count, 0.6×10^9/L) due to enteric loss. Levels of all serum proteins, including immunoglobulins, are decreased. Small-bowel radiographs show edematous folds, and small-bowel biopsy specimens show dilated lacteals and lymphatics in the lamina propria that may contain lipid-laden macrophages. The same biopsy findings are seen in obstruction of mesenteric lymph nodes (lymphoma, Whipple disease, and Crohn disease) and obstruction of venous inflow to the heart (constrictive pericarditis and severe right-sided heart failure). Diagnosis is based on abnormal small-bowel biopsy findings and enteric protein loss documented by finding increased α_1-antitrypsin levels in the stool.

Treatment is with a low-fat diet and medium-chain triglycerides (they enter the portal blood rather than the lymphatics). Occasionally, surgical excision of the involved segment is useful if the lesion is localized.

Amyloidosis

Amyloidosis is characterized by diffuse deposition of amorphous eosinophilic extracellular protein in the tissue. Gastrointestinal tract involvement can occur with AL amyloidosis, AA amyloidosis, and hereditary amyloidosis. The main sites of amyloid deposition are the walls of blood vessels and the mucous membranes and muscle layers of the intestine. Any portion of the gut may be involved. Amyloid damages tissues by infiltration (muscle and nerve infiltration causes motility disorders and malabsorption) and ischemia (obliteration of vessels causes ulceration and bleeding). Intestinal dysmotility can produce diarrhea, constipation, pseudo-obstruction, megacolon, and fecal incontinence. Clinical findings in patients who have amyloidosis include macroglossia, hepatomegaly, cardiomegaly, proteinuria, and peripheral neuropathy. Pinch (posttraumatic) purpura or periorbital purpura after proctoscopic examination may occur.

Small-bowel radiography shows symmetrical, sharply demarcated thickening of the plicae circulares. Histologic examination of duodenal biopsy specimens shows amyloid deposits in up to 100% of patients and is the diagnostic test of choice when amyloid is suspected as a cause of gastrointestinal tract symptoms. Amyloid deposits may not be seen on routine histologic stains; Congo red staining is required. Subcutaneous fat pad aspirate stained with Congo red can be used to make the diagnosis in 80% of patients.

Miscellaneous Small-Bowel Disorders

Meckel Diverticulum

A Meckel diverticulum results from persistence of the vitelline duct, which is the communication between the intestine and the yolk sac. Persistence of the vitelline duct is the most frequent congenital abnormality of the small intestine and is an antimesenteric outpouching of the ileum usually occurring within 100 cm of the ileocecal valve. Because a Meckel diverticulum contains all layers of the intestinal wall, it is a true diverticulum. It may contain ectopic gastrointestinal tract mucosa, including gastric (most commonly), duodenal, biliary, colonic, or pancreatic tissue.

The most common manifestation is painless, maroon stools. Acid production by the ectopic gastric mucosa within the Meckel diverticulum causes peptic ulceration and bleeding. Other manifestations include intestinal obstruction due to intussusception or volvulus around the band that fixes the diverticulum to the bowel wall. Diverticulitis of a Meckel diverticulum can occur and mimic acute appendicitis.

The diagnostic test of choice is a Meckel scan (a technetium Tc 99m pertechnetate nuclear scan, with mucous cells of gastric mucosa concentrating technetium), but false-positive and false-negative results can occur.

Aortoenteric Fistula

If a patient has a history of gastrointestinal tract bleeding and has had a previous aortic graft, immediate evaluation is required to rule out an aortoenteric fistula. Patients with massive gastrointestinal tract bleeding should not undergo endoscopy or arteriography. Emergency surgery is indicated.

Management of a smaller bleeding episode is more controversial, and urgent computed tomography or extended upper endoscopy has been suggested as a possible alternative to surgical exploration. If the presence of a graft fistula is confirmed (by air in the vessel wall on computed tomography or erosion of a graft into the intestinal lumen on endoscopy), emergent surgery is indicated.

KEY FACTS

- ✓ Celiac disease—Howell-Jolly bodies from splenic atrophy (in 10%-15% of patients)
- ✓ Complication of celiac disease—enteropathy-associated T-cell lymphoma (suspect with recurrence of celiac disease after several years of good dietary control)
- ✓ Diagnosis of Whipple disease—upper endoscopy with mucosal biopsy
- ✓ Amyloidosis—amyloid deposits in duodenal biopsy specimens
- ✓ Meckel diverticulum—painless, maroon stools; ectopic gastric mucosa in the diverticulum causes peptic ulceration and bleeding
- ✓ Aortoenteric fistula—consider this possibility immediately if the patient has a history of gastrointestinal tract bleeding and previous aortic graft

Chronic Intestinal Pseudo-obstruction

Pseudo-obstruction is a syndrome characterized by the clinical finding of mechanical bowel obstruction without occlusion of the lumen. The 2 types are primary and secondary.

The primary type, also called *idiopathic pseudo-obstruction*, is a visceral myopathy or neuropathy. It is associated with recurrent bouts of nausea, vomiting, cramping abdominal pain, distention, and constipation, which are of variable frequency and duration. In familial causes, the patient has a positive family history and the condition is present when the patient is young. Esophageal motility is abnormal (achalasia) in most patients; occasionally, urinary tract motility is abnormal. Diarrhea or steatorrhea results from bacterial overgrowth. Upper gastrointestinal tract and small-bowel radiographs show dilatation of the bowel and slow transit (not mechanical obstruction).

Secondary pseudo-obstruction occurs in the presence of underlying systemic disease or precipitating causes (Box 20.1).

If a patient has chronic intestinal pseudo-obstruction, a mechanical cause for the obstruction must first be ruled out. Second, an underlying precipitating cause should be sought, such as metabolic abnormalities, medications, or an underlying associated disease. If a familial idiopathic cause is suspected, esophageal motility should be assessed. Scleroderma may be suspected if intestinal radiography shows large-mouth diverticula of the small intestine. Amyloidosis may be suspected if the skin shows palpable purpura and if proteinuria and neuropathy are present.

Box 20.1 • Causes of Secondary Pseudo-obstruction

Diseases involving intestinal smooth muscle: amyloidosis, scleroderma, systemic lupus erythematosus, myotonic dystrophy, and muscular dystrophy

Neurologic diseases: Parkinson disease, Hirschsprung disease, Chagas disease, and familial autonomic dysfunction

Endocrine disorders: hypoparathyroidism

Drugs: antiparkinsonian medications (levodopa), phenothiazines, tricyclic antidepressants, ganglionic blockers, clonidine, and narcotics

21 Esophageal and Gastric Disorders

CADMAN L. LEGGETT, MD

Esophagus

Esophageal Function

The main functions of the esophagus are to transport food and prevent reflux. To transport food from the mouth to the stomach, the esophagus must work against a pressure gradient, with negative pressure in the chest and positive pressure in the abdomen. The lower esophageal sphincter (LES) helps to prevent reflux of gastric contents back into the esophagus.

The upper esophageal sphincter (UES), consisting of the cricopharyngeus muscle, and the muscle of the proximal one-third of the esophagus are striated muscle. A transition from skeletal to smooth muscle occurs in the midesophagus, with the distal one-third of the esophagus composed of smooth muscle under involuntary control. The LES is a zone of circular muscle located in the distal 2 to 3 cm of the esophagus.

Normal Motility

Immediately after a person swallows, the UES relaxes, which allows a food bolus to pass from the oropharynx into the esophagus. A peristaltic wave then propagates through the body of the esophagus. The LES relaxes shortly after initiation of the swallow to allow passage of the food bolus into the stomach and then contracts and maintains resting tone to prevent reflux. If the esophagus cannot perform its 2 main functions, symptoms of dysphagia or reflux may result.

Dysphagia

Dysphagia results from defective transport of food and is usually described as "difficulty swallowing" or "food sticking." Three causes of dysphagia must be distinguished: 1) oropharyngeal dysphagia (faulty transfer of a food or fluid bolus from the oropharynx into the esophagus); 2) motor dysphagia (due to an underlying motility disorder); and 3) mechanical dysphagia (structural abnormality of the esophageal lumen).

The answers to 3 questions can help in making the diagnosis (Figure 21.1): 1) What types of food produce the dysphagia (solids, liquids, or both)? 2) What is the time course of the dysphagia (intermittent or progressive)? 3) Is there associated heartburn?

Esophagogastroduodenoscopy (EGD) is the test of choice for all patients with dysphagia unless features of oropharyngeal dysphagia are present (see below).

Oropharyngeal Dysphagia

Oropharyngeal dysphagia is the result of faulty transfer of a food bolus from the oropharynx into the esophagus and is most commonly caused by neuromuscular disorders and less commonly by proximal structural abnormalities (Box 21.1). In addition to having difficulty swallowing, patients with oropharyngeal dysphagia report coughing, choking, aspiration pneumonia, or nasal regurgitation with eating or drinking. The first test in the evaluation of oropharyngeal dysphagia is a video fluoroscopic swallowing test (also called a modified barium swallow). After oropharyngeal dysphagia is diagnosed, an evaluation to determine the underlying cause is needed; the diagnosis may be suggested by associated features such as optic neuritis (with multiple sclerosis) or fatigability (with myasthenia gravis).

Key Definition

Oropharyngeal dysphagia: *faulty transfer of a food bolus from the oropharynx into the esophagus.*

The editors and authors acknowledge the contributions of Amy S. Oxentenko, MD, to the previous edition of this chapter.

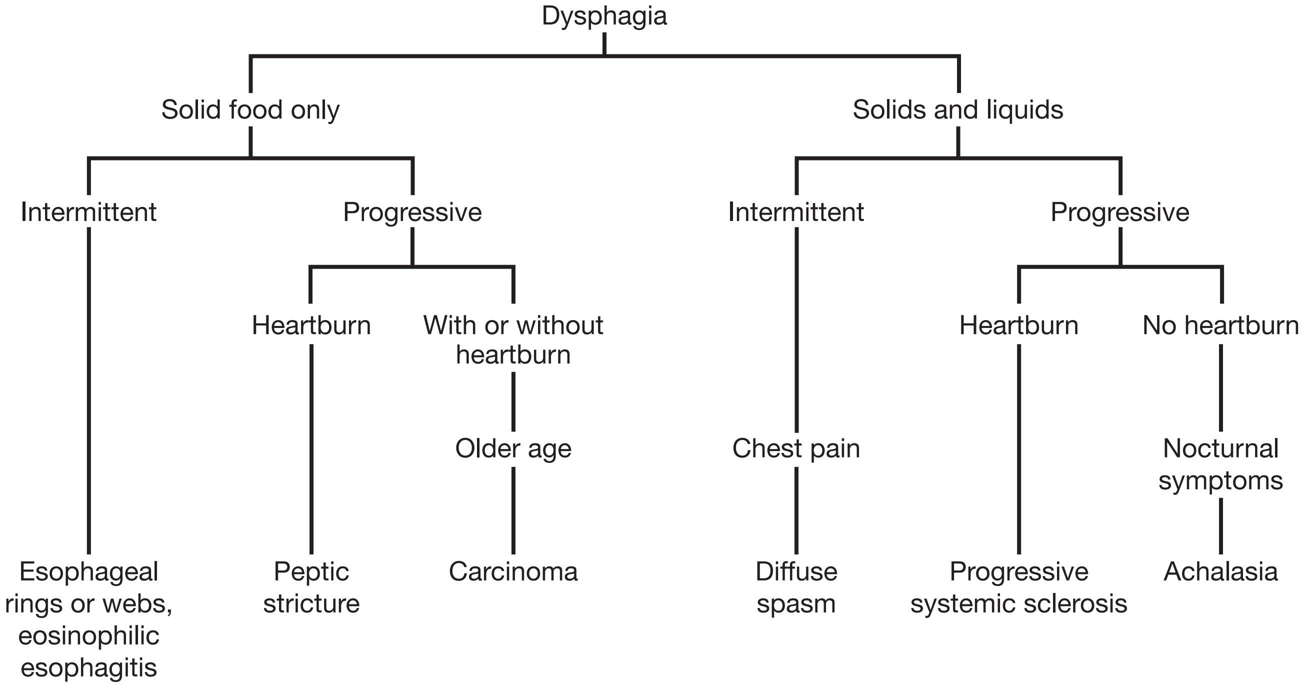

Figure 21.1. *Diagnostic Scheme for Dysphagia. The answers to 3 questions (see text) often suggest the most likely diagnosis.*
(Modified from MKSAP VI: part 1:44, 1982. American College of Physicians; used with permission.)

Motor Dysphagia

Motor (or *motility*) *disorders* are characterized by dysphagia with both solids and liquids. These disorders may follow an intermittent or progressive course. The 3 important motor abnormalities of the esophagus are achalasia, scleroderma, and diffuse esophageal spasm.

Achalasia

The term *achalasia* means "failure to relax." It results from degeneration of the myenteric plexus in the esophageal body and LES. Patients have years of progressive dysphagia to both solids and liquids. Although these patients may have regurgitation of undigested and fermented food that never passed out of the esophagus (as evidenced by the presence of regurgitated food on their pillow after sleeping), heartburn is typically absent because the tonically contracted LES prevents acid from entering the esophagus. Chest radiography may show an air-fluid level within the esophagus in advanced cases. Barium esophagography typically shows a dilated esophagus with a pointed ("bird beak") tapering at the LES. High-resolution esophageal manometry is the diagnostic test of choice for achalasia; it is characterized by findings of 1) incomplete relaxation of the LES, 2) increased resting tone of the LES, and 3) aperistalsis of the esophageal body. All patients with features of achalasia require EGD because cancer infiltrating near the esophagogastric junction may have the same radiographic and manometric pattern of achalasia (termed *pseudoachalasia*). Patients with pseudoachalasia tend to be older, have more rapid onset of symptoms (months rather than years), and have more profound weight loss. Treatment of achalasia includes surgical or endoscopic myotomy, injection of botulinum toxin into the LES, or pneumatic dilation. Healthy patients should be considered for myotomy. Botulinum toxin injection into the LES decreases lower esophageal pressure for approximately 3 months and therefore should be considered for elderly patients and for patients with high surgical risk. In Brazil, the parasite *Trypanosoma cruzi* (which causes Chagas disease) produces a neurotoxin that destroys the myenteric plexus and leads to esophageal dilatation identical to that of achalasia.

Scleroderma

Esophageal involvement with *scleroderma* is associated with the CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias). Patients have chronic, progressive dysphagia with both solids and liquids, along with severe heartburn and reflux. Barium swallow fluoroscopy may show a rigid esophagus and a widely patent LES. Although motility testing shows aperistalsis in the body of the esophagus similar to achalasia, the decreased LES tone in scleroderma distinguishes the 2 conditions.

Diffuse Esophageal Spasm

Patients with *diffuse esophageal spasm* usually have chest pain, but they also may have intermittent dysphagia with solids or liquids (or both); symptoms may be aggravated by stress, hot or cold liquids, and carbonated beverages. Imaging may show a

Box 21.1 • Causes of Oropharyngeal Dysphagia

- Muscular disorders
  - Amyloidosis
  - Dermatomyositis
  - Hyperthyroidism
  - Hypothyroidism
  - Myasthenia gravis
  - Myotonia dystrophica
  - Oculopharyngeal myopathy
  - Stiff man syndrome
- Neurologic disorders
  - Amyotrophic lateral sclerosis
  - Multiple sclerosis
  - Parkinson disease
  - Polio
  - Stroke
  - Tabes dorsalis
  - Tetanus
- Structural causes
  - Cervical osteophytes
  - Cricopharyngeal dysfunction
  - Esophageal webs
  - Goiter
  - Lymphadenopathy
  - Zenker diverticulum

corkscrew esophagus. Motility studies may demonstrate simultaneous contractions throughout the body of the esophagus during symptoms. A trial of acid suppression should be considered because acid reflux may precipitate esophageal spasm in some persons.

KEY FACTS

✓ Dysphagia has 3 causes—oropharyngeal, motor, and mechanical

✓ EGD—diagnostic test of choice for mechanical dysphagia or motor dysphagia

✓ Achalasia—EGD is required for ruling out pseudoachalasia (cancer near the esophagogastric junction)

✓ Scleroderma and achalasia—the body of the esophagus is aperistaltic in both conditions, but the LES tone is decreased in scleroderma

Mechanical Dysphagia

Dysphagia can result from compromise of the esophageal lumen to a diameter of less than 12 mm. This type of dysphagia usually begins with solid foods, but it may progress to involve liquids with further luminal narrowing. Depending on the cause, such as cancer, weight loss may occur.

Peptic Strictures

A *peptic stricture* results from repeated esophageal reflux of acid. It is usually a short (<2 cm) narrowing in the distal esophagus immediately at or above the esophagogastric junction. Management includes esophageal dilation and long-term acid suppression; proton pump inhibitor (PPI) therapy after dilation of a peptic stricture has been proved to decrease recurrence.

Alkali-Induced Strictures

Alkali is more injurious to the esophagus than acid. *Alkali-induced strictures* can occur in patients after a total or partial gastrectomy or after lye ingestion. Inducing emesis after lye ingestion is contraindicated because the caustic substance can reinjure the esophagus with subsequent exposure. Lye-induced strictures tend to be long (compared with peptic strictures). Repeated dilation or temporary stenting of the esophagus is often required after an alkali-induced stricture has occurred. Patients with lye-induced strictures have an increased incidence of squamous cell cancer of the esophagus.

Rings, Webs, and Diverticula

A *lower esophageal ring* (also called a Schatzki ring) is a constriction at the esophagogastric junction. The rings tend to cause intermittent solid food dysphagia or impaction, most notably with foods such as meat and bread (hence the name "steak house syndrome"). Esophageal dilation is the treatment of choice.

An *esophageal web* consists of a squamous membrane that can be found throughout the esophagus, which leads to dysphagia. If patients have an esophageal web with a proximal location, they can have features of oropharyngeal dysphagia.

The *Plummer-Vinson syndrome* occurs in women who have iron-deficiency anemia, glossitis, and proximal esophageal webs. They have an increased risk of squamous cell carcinoma of the esophagus.

Zenker diverticulum, an outpouching adjacent to the UES, results from increased tone within the UES. Patients have dysphagia, regurgitation of small amounts of old food, and halitosis. Fullness in the neck may be apparent. Barium esophagography should be performed if there is clinical suspicion for Zenker diverticulum. Management includes resection of the diverticulum in combination with UES myotomy.

Eosinophilic Esophagitis

Patients with *eosinophilic esophagitis* have intermittent solid food dysphagia and food impactions. It occurs most commonly in young men, but it may occur in all ages and in either sex. The patient may have a personal or family history of atopic conditions (eg, asthma, eczema, or seasonal allergies). Endoscopic findings may include concentric esophageal rings, furrows, or a featureless narrowed esophagus; some patients have normal findings. The diagnosis is established by finding more than 15 eosinophils per high-power field on midesophageal biopsies. Initial management is with a PPI trial, which may improve symptoms in some patients with esophageal eosinophilia. For patients who have persistent symptoms despite acid suppression, swallowed, aerosolized corticosteroids are recommended. Recurrent symptoms are not uncommon after treatment. For children, elimination diets may be used. Severe tears can occur in untreated patients, so dilation of any associated strictures should be considered only after medical therapy has begun.

Esophageal Cancer

Squamous cell carcinomas of the esophagus are usually located in the proximal two-thirds of the esophagus, whereas tumors of the distal one-third are more commonly adenocarcinoma. The conditions that predispose to esophageal squamous cell carcinoma include achalasia, lye-induced stricture, Plummer-Vinson syndrome, human papillomavirus infection, tylosis, smoking, and alcohol consumption. Barrett esophagus is the established precursor to adenocarcinoma of the esophagus. In the United States (US), most esophageal cancers are adenocarcinoma. Progressive dysphagia accompanied by weight loss is typical. The diagnosis is established by endoscopy with biopsy. After the diagnosis is confirmed, computed tomography of the chest and abdomen is recommended to evaluate for metastatic disease. Endoscopic ultrasonography may be used to assess locoregional staging after distant metastases have been ruled out. The 5-year survival rate is only 7% to 15% because most patients have advanced disease at initial evaluation.

Surgical resection is the treatment of choice for early-stage esophageal cancer. For patients with locally advanced disease or lymph node involvement, preoperative chemoradiotherapy may be considered, with restaging thereafter. For patients with extensive nodal or metastatic disease, palliative therapy can be offered, including chemotherapy, radiotherapy, and esophageal stenting.

Odynophagia

Odynophagia refers to painful swallowing. It results most commonly from inflammation (related to infection or medication) or spasm.

Key Definition

Odynophagia: *painful swallowing.*

Infections of the Esophagus

Patients with immunodeficiency disorders (eg, acquired immunodeficiency syndrome), diabetes mellitus, cancers (especially lymphoma and leukemia), or esophageal motility disorders are susceptible to opportunistic infections of the esophagus and may have odynophagia. The most important infections to recognize are those caused by *Candida albicans* (the most common cause), herpesvirus, or cytomegalovirus.

With candidal infection, endoscopy shows cottage cheese–like plaques adherent to the esophageal mucosa. The diagnosis is made by demonstrating pseudohyphae microscopically from brushings of the mucosa. Treatment is with oral fluconazole for *Candida* esophagitis. For patients with odynophagia who have evidence of thrush, therapy with oral fluconazole may be empirically started for presumed *Candida* esophagitis, with endoscopy reserved for those in whom empirical therapy fails. If thrush is not present, patients should undergo endoscopy to establish a diagnosis unless there is a clear association with a medication.

If patients have herpesvirus infection, endoscopy may show multiple, small, discrete ulcers, with biopsies from the edge of the ulcers revealing intranuclear inclusions and surrounding halos and multinucleated giant cells. Treatment is with acyclovir. In cytomegaloviral infection, endoscopy may show large, irregular ulcers, with biopsies from the ulcer base showing "owl's eye" intranuclear inclusions and enlarged areas of cytoplasm. Treatment is with ganciclovir or foscarnet (in cases resistant to ganciclovir).

Medication-Induced Esophagitis

Patients with *medication-induced esophagitis* have odynophagia (or, less frequently, dysphagia). Medication-induced esophagitis may occur if esophageal motility or anatomy is abnormal, but it occurs more frequently if medications are not taken with adequate fluids or if patients assume a supine position immediately after taking them. Medications commonly associated with esophagitis include tetracycline, doxycycline, quinidine, potassium supplements, bisphosphonates, ferrous sulfate, ascorbic acid, and nonsteroidal anti-inflammatory drugs (NSAIDs). Stopping use of the medication for several days is often all that is needed, with clear instructions for administration if the medication is resumed. The use of these medications should be avoided if possible in patients with known esophageal strictures or dysphagia.

KEY FACTS

- ✓ Alkali causes more esophageal damage than acid
- ✓ Alkali-induced strictures—after gastrectomy (total or partial) or lye ingestion
- ✓ Eosinophilic esophagitis—intermittent solid food dysphagia and food impactions; midesophageal biopsy shows >15 eosinophils per high-power field
- ✓ Esophageal infections—most important ones are caused by *Candida albicans* (most common), herpesvirus, or cytomegalovirus

Gastroesophageal Reflux Disease

Reflux

Gastroesophageal reflux disease (GERD) is typically caused by inappropriate relaxation of the LES or by intragastric pressure that exceeds the LES pressure. Complications of reflux include esophagitis, bleeding, stricture formation, aspiration, Barrett esophagus, and adenocarcinoma of the esophagus.

Most patients with GERD describe classic heartburn or regurgitation. Atypical symptoms of GERD include noncardiac chest pain, asthma, chronic cough, hoarseness, and enamel defects. Reflux is the most common cause of noncardiac chest pain; however, it is imperative that cardiac status be evaluated before chest pain is attributed to reflux. Patients with asthma and coexisting reflux should receive therapy for reflux because it may improve control of respiratory symptoms. Reflux should be considered in patients with asthma who have postprandial or nocturnal wheezing.

Tests for Reflux

For patients with classic symptoms of reflux and heartburn with no alarm features (weight loss, anemia, dysphagia, odynophagia, or family history of cancer in the upper gastrointestinal tract), an empirical trial of PPI therapy is warranted. However, testing should be performed if patients have atypical features, symptoms refractory to a PPI trial, long-standing symptoms, or alarm features. The initial test in the evaluation of these symptoms should be EGD. If esophagitis is present, reflux can be diagnosed with certainty. However, 40% of patients may have symptomatic reflux with no gross inflammation.

If EGD does not show esophagitis or other features to support the diagnosis of reflux, a 24-hour ambulatory pH probe with impedance monitoring can be used to document esophageal acid exposure and symptom correlation. This allows for a physiologic evaluation of reflux during daily activities. The test is valuable for patients who have had upper endoscopic results that are nondiagnostic (ie, no esophagitis is noted) and have ongoing or atypical features. Impedance technology, which has been added to standard 24-hour pH monitoring, allows for the detection of non–acid reflux events that may be symptomatic and is useful in patients who have symptoms despite PPI therapy.

Barium esophagography is not useful in the evaluation of reflux, because reflux of barium occurs in 25% of controls. This test can be helpful in clarifying abnormal anatomical features (eg, paraesophageal hernia, intrathoracic stomach, and complicated strictures) but should not replace upper endoscopy.

Treatment of Reflux

The management of GERD is usually stepwise. Patients should be counseled on lifestyle modifications: The head of the patient's bed should be elevated 15 cm to keep the stomach lower than the esophagus, and patients should be advised to not eat for 3 hours before reclining, to lose weight if overweight, to avoid eating foods that personally trigger symptoms (eg, fatty foods, chocolate, peppermint, citrus juices, tomato products, and coffee), and to avoid tobacco and alcohol. In addition, patients should avoid drugs that decrease LES pressure or delay gastric emptying (eg, anticholinergic agents, opioids, progesterone-containing agents, nitrates, and calcium channel blockers).

Medical therapy for reflux is graduated according to the severity of the patient's symptoms. Over-the-counter antacids or H_2-receptor antagonists may be helpful for patients with occasional heartburn and reflux related to a triggering meal. PPIs (eg, omeprazole) are the most effective agents to relieve symptoms and promote mucosal healing. Long-term use of these agents, however, is associated with an increased risk of community-acquired pneumonia and *Clostridioides difficile* (formerly known as *Clostridium difficile*) infection. Although retrospective studies suggest an association between PPIs and conditions such as osteoporosis, chronic kidney disease, and dementia, there is insufficient evidence to suggest causality. A PPI regimen should be tailored to the minimum dose that leads to resolution of symptoms. Patients may take these medications once or twice daily, optimally 30 to 60 minutes before a meal. For patients with esophagitis, long-term PPI use is needed to allow for healing and to prevent future complications such as a peptic stricture.

Antireflux surgery can be considered for younger patients who respond to PPI therapy but want to avoid lifelong medical treatment. Nissen fundoplication is the preferred operation. Those who do not respond to medical therapy are unlikely to have relief of symptoms after surgery. Those with dysphagia and bloating should avoid surgery, because both of these symptoms can occur or worsen after antireflux surgery. Patients with scleroderma should not have antireflux surgery because esophageal aperistalsis would lead to severe postoperative dysphagia.

Barrett Esophagus

Barrett esophagus is a consequence of chronic GERD in which the normal esophageal squamous mucosa is replaced by intestinal metaplasia. Patients with Barrett esophagus are at increased risk for adenocarcinoma. Most experts recommend screening endoscopy for high-risk patients (obese white men older than 50 years) who have had chronic reflux for more than 5 years. If mucosal changes are seen endoscopically, biopsies are needed to confirm the diagnosis and to look for dysplasia. The surveillance frequency is based on the presence and degree of dysplasia found during the previous study. If high-grade dysplasia is identified and confirmed by 2 pathologists, the patient may elect to undergo esophagectomy or be considered for endoscopic therapy (ablation, mucosal, resection, or both).

Noncardiac Chest Pain

All patients with chest pain should be thoroughly evaluated to rule out a potential cardiac cause before other diagnoses are considered. GERD is the most common cause of noncardiac chest pain, but esophageal pain may be due to a motor disorder (eg, spasm) or esophageal inflammation (eg, infection or injury). Esophageal spasm can closely mimic angina. EGD is used to rule out mucosal disease (eg, inflammation, neoplasm, or chemical injury). A 24-hour ambulatory pH probe with impedance can be used to document the presence of reflux and its correlation with chest pain. Therapy for noncardiac chest pain includes avoidance of precipitants. PPIs may be beneficial for patients with reflux. Nitroglycerin (short or long acting) or calcium channel blockers are sometimes helpful in motor disorders. If appropriate, reassurance that cardiac disease is not present may be all that is necessary.

Other Esophageal Problems

Mallory-Weiss Tear

A **Mallory-Weiss tear** is a mucosal laceration at the esophagogastric junction. It accounts for about 10% of the cases of upper gastrointestinal tract bleeding; most patients have a history of retching or vomiting before the bleeding begins (eg, hyperemesis gravidarum, alcohol intoxication, or bulimia). The bleeding stops spontaneously in 90% of patients, but endoscopic hemostatic techniques can be used if needed.

Key Definition

Mallory-Weiss tear: *a mucosal laceration at the esophagogastric junction.*

Esophageal Perforation

Esophageal perforation most commonly occurs after dilation of a stricture or in the setting of esophageal cancer. Spontaneous perforation of the esophagus (Boerhaave syndrome) occurs after violent retching. The most common site of perforation is the left posterior aspect of the distal esophagus. If pleural fluid is present, it may have an increased concentration of amylase. The cervical esophagus may be perforated if a Zenker diverticulum is inadvertently intubated for EGD or nasogastric tube placement.

KEY FACTS

- ✓ Causes of GERD—1) inappropriate LES relaxation or 2) intragastric pressure greater than LES pressure
- ✓ Complications of GERD—esophagitis, bleeding, stricture formation, aspiration, Barrett esophagus, and adenocarcinoma of the esophagus
- ✓ Empirical trial of PPI therapy—for patients with classic symptoms of reflux and heartburn but no alarm features
- ✓ Antireflux surgery (Nissen fundoplication)—for younger patients who respond to PPI therapy and want to avoid lifelong medical treatment

Stomach and Duodenum

Peptic Ulcer Disease

Peptic ulcers are defects in the gastric or duodenal mucosa that result from an imbalance between acid and pepsin in the gastric juice and the host's protective mechanisms. Stimulators of acid production include acetylcholine, histamine, and gastrin. Inhibitors of gastric acid production include somatostatin and prostaglandin.

Peptic ulcers are categorized as being associated with 3 causative factors: 1) *Helicobacter pylori*; 2) NSAIDs, including aspirin; or 3) miscellaneous. At least 90% of peptic ulcers are due to either *H pylori* or NSAIDs. Miscellaneous causes include gastrinomas (Zollinger-Ellison syndrome), Crohn disease, cancer, drugs (cocaine), and viral infections (cytomegalovirus). There is no evidence that smoking or corticosteroids cause peptic ulcer disease (PUD), but either can result in decreased ulcer healing and increased complications.

Infection with *H pylori* causes more duodenal ulcers than gastric ulcers. Although NSAIDs tend to cause more gastric ulcers than duodenal ulcers, *H pylori* infection is still more likely to account for gastric ulcer disease in general.

Certain medical conditions may predispose to stress-induced peptic injury: ventilator use, underlying coagulopathy, severe burns, or central nervous system injury. Patients with these conditions should be considered candidates for prophylactic therapy.

Helicobacter pylori

The Organism

A gram-negative, spiral-shaped bacillus, *H pylori* is commonly acquired through oral ingestion and transmitted among persons living in close quarters. This fastidious organism resides and multiplies beneath and within the mucous layer of the gastric mucosa and produces several enzymes, such as urease, important for its survival and pathogenic effects.

Helicobacter pylori infection can lead to gastritis (acute to chronic), PUD, atrophic gastritis, mucosa-associated lymphoid tissue (MALT) lymphoma, or gastric cancer.

Epidemiology

In the US, the prevalence of *H pylori* varies by age, occurring in 10% of the general population younger than 30 years and in 60% of persons older than 60 years. Overall, *H pylori* is more prevalent among black and Hispanic persons, poorer socioeconomic groups, and institutionalized persons. In developing countries, 50% of the population is infected by age 10 years and 70% by 20 years, with 85% to 95% of the population infected overall. Evidence of person-to-person transmission exists.

Associated Diseases

Chronic Active Gastritis

The most common cause of chronic active gastritis is *H pylori* infection. The infection is predominantly an antral-based gastritis, although gastritis throughout the gastric body may be seen.

Duodenal Ulcer

In approximately 80% of patients with duodenal ulcers, *H pylori* is present. Among *H pylori*–positive patients with a duodenal ulcer who do not receive treatment targeted at the organism, most have ulcer relapse within 1 year. However, if the infection is successfully eradicated, the rate of relapse is extremely low.

Gastric Ulcer

In more than 50% of patients with gastric ulcers, *H pylori* is present. Eradication of the bacteria decreases the relapse rate of gastric ulcers.

Gastric Tumors

A known carcinogen as identified by the World Health Organization, *H pylori* is the leading cause of gastric cancer in the world. The gastric cancer that results from *H pylori* infection is due to a progression from chronic gastritis to atrophic gastritis, to metaplasia, to dysplasia, and eventually to gastric adenocarcinoma.

MALT Lymphoma

MALT lymphoma of the stomach is a low-grade B-cell lymphoma. The majority of cases (90%) are related to *H pylori* infection. For early-stage disease, simple eradication of *H pylori* infection can induce complete or partial remission. For patients with more advanced disease, traditional lymphoma therapy is recommended.

Functional Dyspepsia

Functional dyspepsia, also known as nonulcer dyspepsia, is common, affecting about 20% of the US population. Among persons with functional dyspepsia, up to 50% may be infected with *H pylori*; however, dyspepsia clinically improves with eradication therapy in only a small percentage of patients. Patients with functional dyspepsia often report postprandial fullness, early satiation, epigastric pain, or a combination of these. The diagnosis of functional dyspepsia is considered once organic causes such as GERD, *H pylori* infection, and gastroparesis are ruled out. Patients with functional dyspepsia may benefit from PPIs. If symptoms persist, a neuromodulator such as a low-dose tricyclic antidepressant can be used.

Diagnostic Tests for H pylori Infection

Various diagnostic tests are available for *H pylori* infection. The choice of test is determined by the need for endoscopy, the use of certain medications, and cost (Table 21.1). For patients who need to be assessed for *H pylori* infection but do not require endoscopy, noninvasive evaluation with serologic antibody, stool antigen, or urea breath testing can be performed. The best noninvasive tests for determining eradication are the stool antigen test and the urea breath test.

Serologic Testing

Serologic testing is one of the most cost-effective, noninvasive ways to diagnose primary *H pylori* infection, and it is the only test for *H pylori* that is not affected by medications the patient may be taking. It is useful only in making the initial diagnosis, however, and should not be used for eradication testing.

Urea Breath Test

For the urea breath test, a radiolabeled dose of urea is given orally to the patient. If *H pylori* is present, the urease activity splits the urea, and radiolabeled carbon dioxide is exhaled.

Stool Antigen Test

The *H pylori* stool antigen test is simple and noninvasive. Unlike serologic testing, stool antigen testing does not depend on disease prevalence.

Table 21.1 • Tests for Detecting Helicobacter pylori

Test	Advantages	Disadvantages
Serologic testing	Easy to perform Good negative predictive value Not affected by medications	Dependent on prevalence Indicates past infection only (not used for eradication)
Stool antigen	Indicates active infection Useful for primary or eradication testing	Stool collection Can be affected by antibiotics, acid suppression, or bismuth
Urea breath test	Indicates active infection Useful for primary or eradication testing	Can be affected by antibiotics, acid suppression, or bismuth
Rapid urease test	Quick results	Expense of endoscopy Can be affected by antibiotics, acid suppression, or bismuth
Histologic evaluation	Allows for evaluation of histologic changes (eg, dysplasia)	Expense of endoscopy Dependent on expertise of pathologist

Rapid Urease Test

For the rapid urease test, a biopsy specimen taken during EGD is impregnated into agar that contains urea and a pH indicator. As the urea is split by *H pylori*–produced urease, the pH of the medium changes the color of the agar. This test depends on bacterial urease: The more organisms present, the more rapidly the test produces positive results.

Histologic Examination

The *H pylori* organisms can be demonstrated with several specialized stains, including hematoxylin-eosin, Warthin-Starry, and immunostaining.

Treatment

With an *H pylori*–positive duodenal or gastric ulcer, the treatment goal is to heal the ulcer and eradicate the bacteria. All patients who are infected with *H pylori* should receive combination therapy. PPI-based triple therapy (usually in combination with amoxicillin and clarithromycin) for 10 to 14 days is the most commonly used initial therapy; metronidazole can be used in place of amoxicillin in patients who have a penicillin allergy. Because of emerging patterns of resistance to clarithromycin and metronidazole, these agents should be avoided if subsequent treatment is necessary and they were used as initial therapy. If the first course of therapy fails to eradicate the organism, quadruple therapy can be considered (PPI, metronidazole, bismuth, and tetracycline). Sequential therapy has also been used.

KEY FACTS

- ✓ Stress-induced peptic injury—prophylactic therapy should be considered for patients with ventilator use, coagulopathy, severe burns, or central nervous system injury
- ✓ Prevalence of *H pylori* in the US general population—10% in persons younger than 30 years; 60% in persons older than 60 years
- ✓ Best noninvasive tests for determining eradication of *H pylori*—stool antigen test and urea breath test

NSAID-Induced Ulcers

NSAIDs inhibit gastroduodenal prostaglandin synthesis, which results in decreased secretion of mucus and bicarbonate, reduced mucosal blood flow, and stimulated acid production. NSAID-induced ulcers occur more commonly in the stomach (typically in the antrum) than in the duodenum.

The risk of PUD with NSAIDs is dose dependent. Higher doses of NSAIDs or the combination of 2 or more NSAIDs (including low-dose aspirin) increases the risk of gastrointestinal tract injury. Selective cyclooxygenase 2 (COX-2) inhibition has been shown to decrease the rate of PUD and ulcer complications, such as bleeding, perforation, and pain. However, data suggest that even low-dose aspirin can reduce or eliminate any protective benefit of selective COX-2 drugs. For patients who require NSAID therapy, the lowest possible dose should be used and combination NSAID therapy avoided. The risk of PUD with NSAID initiation is maximal in the first month of treatment, and elderly patients and patients with a previous history of PUD are at highest risk.

The first step in the treatment of an NSAID-induced ulcer is to discontinue use of the drug if feasible. PPIs are most effective in healing and preventing ulcers and have few adverse effects. The synthetic prostaglandin agonist misoprostol decreases the incidence of NSAID-induced gastric ulcers; however, its usefulness is limited by the adverse effect of diarrhea and its role as an abortifacient (it should be avoided in women of childbearing age).

Zollinger-Ellison Syndrome

Zollinger-Ellison syndrome is characterized by acid hypersecretion and the triad of peptic ulceration, esophagitis, and diarrhea (because excess acid inactivates pancreatic lipase) caused by a gastrin-producing tumor. The tumor usually is located in the "gastrinoma triangle," which includes the head of the pancreas, duodenal wall, and distal common bile duct. Two-thirds of gastrinomas are malignant and can metastasize. One-fourth of gastrinomas are related to multiple endocrine neoplasia type 1 (MEN-1) and are associated with pituitary adenomas and hyperparathyroidism.

Zollinger-Ellison syndrome should be considered in patients with *H pylori*–negative, NSAID-negative PUD, especially if there are multiple ulcers, ulcers in unusual locations (postbulbar duodenum), or refractory ulcers. Increased serum gastrin levels (>1,000 pg/mL) in patients who produce gastric acid are essentially diagnostic of gastrinoma. Increased serum gastrin levels may also be present in patients who are receiving PPI therapy (the most common reason) or who have atrophic gastritis (the next most common reason), pernicious anemia, postvagotomy states, or gastric outlet obstruction. Basal gastric acid output studies could be performed for patients who have increased levels of gastrin to assess for acid hypersecretion or achlorhydria. If the laboratory results are equivocal, a secretin test could be performed, if available; this test produces a paradoxical increase in the serum level of gastrin in patients with gastrinoma.

An octreotide scan (Octreoscan) can be used to localize a gastrinoma owing to the presence of somatostatin receptors. Endoscopic ultrasonography has been successful in localizing gastrinomas because the pancreas and duodenal wall can be easily viewed with this test.

Because 50% of patients with gastrinomas have metastatic disease, curative surgery is not always feasible. Patients who are not candidates for surgery can receive high-dose acid suppression. Those with MEN-1 are usually not considered for surgical resection because of the multifocality of the disease.

Key Definition

Zollinger-Ellison syndrome: *acid hypersecretion with the triad of peptic ulceration, esophagitis, and diarrhea.*

Ulcer Diagnosis and Management

EGD is the best initial test to establish the diagnosis of PUD. At endoscopy, any active bleeding can be managed. Histologic evaluation can be performed if an ulcer has malignant features. If perforation is a concern, abdominal imaging with computed tomography should be the first test (endoscopy would be contraindicated).

A patient who has active bleeding from suspected ulcer disease must be hemodynamically stabilized before endoscopy is performed; endotracheal intubation may be required. PPI therapy should be initiated to stabilize clotting. Endoscopic therapy is selectively used according to stigmata of bleeding. All patients should be assessed for *H pylori* infection and NSAID use.

Angiography may be required for PUD if endoscopic therapy has failed to control active bleeding. Surgical intervention is infrequently needed for bleeding but would be considered if bleeding cannot be controlled angiographically. For perforation, urgent surgical consultation is necessary.

Chronic Gastritis

Chronic gastritis is most often caused by either *H pylori* infection or autoimmune gastritis. The most common cause of chronic gastritis is *H pylori* gastritis, which typically involves the antrum. Gastric ulcers and duodenal ulcers occur commonly, and the incidence of gastric adenocarcinoma is increased. *Helicobacter pylori*–related gastritis also predisposes to MALT lymphoma. If gastric biopsy results yield “chronic active gastritis,” an evaluation for *H pylori* should ensue.

Autoimmune gastritis involves the body and fundus of the stomach (not the antrum). In a subset of patients, atrophic gastritis develops. Pernicious anemia with achlorhydria and megaloblastic anemia may result. Antiparietal cell or anti–intrinsic factor antibodies are found in more than 90% of these patients. Other autoimmune diseases are often present. The serum gastrin level may be markedly increased (given the lack of gastric acid to provide negative feedback) and may give rise to gastric carcinoid tumors, which usually follow an indolent course in these patients. Peptic ulcers do not typically develop in patients with autoimmune gastritis owing to achlorhydria, but the patients are at increased risk for intestinal metaplasia and gastric adenocarcinoma.

Gastric Cancer

In the 1940s, gastric cancer was the most common cancer in the US. Since then, the incidence in the US has decreased substantially. Currently, Japan has the highest mortality rate from gastric cancer. Known risk factors for gastric cancer are *H pylori* infection, autoimmune gastritis, and certain hereditary cancer syndromes. Known dietary risk factors include increased consumption of pickled foods, salted fish, processed meat, smoked foods, and products high in nitrates. The male to female ratio is as high as 2:1. Gastric cancer is more common in lower socioeconomic groups.

Clinical Aspects

Gastric cancer is often asymptomatic in the early stages, becoming symptomatic with advanced disease. The 2 types of gastric cancer are the intestinal type and the infiltrating type. The intestinal type of gastric cancer tends to appear as an ulcerated mass (similar to a cancer of the small or large intestine), with distinct borders and well-differentiated histologic features; patients often have abdominal pain and iron- deficiency anemia. Gastric cancer that is in an infiltrating form, also referred to as *linitis plastica*, often causes early satiety and weight loss because the stomach cannot stretch and accommodate food. The infiltrating form tends to be poorly differentiated and is associated with signet ring cells and a poor outcome. EGD is the initial test of choice to obtain a histologic diagnosis. After the diagnosis is established, computed tomography should be performed to evaluate for metastatic disease.

Treatment and Prognosis

For localized disease, resection with tumor-free margins often requires total gastrectomy. For disseminated disease, surgical treatment is necessary only for palliation. Response to chemotherapy is generally poor. Five-year survival is 90% if the tumor is confined to the mucosa and submucosa, 50% if the tumor is through the serosa, and 10% if the tumor involves regional lymph nodes.

Gastric Polyps

Gastric polyps are common and are typically found incidentally. There are 3 types of polyps: cystic fundic gland, hyperplastic, and adenomatous. *Cystic fundic gland polyps* are the most common gastric polyps and are not premalignant except in association with familial adenomatous polyposis (FAP). No additional therapy is needed unless FAP is known or suspected to be present. *Hyperplastic polyps* may occur with chronic gastritis, so patients should be tested for *H pylori* infection. Hyperplastic polyps rarely have malignant potential. *Adenomatous polyps* are deemed premalignant and must be fully removed (like colon polyps).

The 3 types of carcinoid tumors may manifest as an incidentally noted gastric polyp: *Type 1 gastric carcinoids* are associated with autoimmune gastritis, whereas *type 2 gastric carcinoids* are associated with MEN-1; both forms tend to follow an indolent course. *Type 3 gastric carcinoids* tend to be sporadic and behave aggressively.

Gastroduodenal Dysmotility Syndromes

Gastroparesis

Symptoms of delayed gastric emptying (ie, *gastroparesis*) may include nausea, vomiting, bloating, early satiety, anorexia, and weight loss. Diabetes mellitus is the most common cause of

Box 21.2 • Conditions Causing Gastroparesis

- Acute conditions
  - Medication use (anticholinergic agents, opioids)
  - Hyperglycemia
  - Hypokalemia
  - Pancreatitis
  - Surgical procedures
  - Trauma
  - Viral infections
- Chronic conditions
  - Amyloidosis
  - Diabetes mellitus
  - Gastric dysrhythmias
  - Pseudo-obstruction
  - Scleroderma
  - Vagotomy

gastroparesis, which can occur with long-standing disease or with substantial fluctuations in serum glucose levels. Other causes of gastroparesis exist (Box 21.2). After mechanical obstruction has been ruled out (usually with upper endoscopy), the test of choice to assess for gastroparesis is a 4-hour gastric scintigraphic study with a solid meal. Any medications known to alter gastric motility, namely opioids, must be discontinued before testing.

Management of gastroparesis includes 1) dietary alterations, 2) antiemetic agents, and 3) prokinetic drugs, if needed. Metoclopramide is a dopamine antagonist and a cholinergic agonist that increases the rate and amplitude of antral contractions. It crosses the blood-brain barrier and can cause drowsiness and galactorrhea (from increased release of prolactin). The most feared complication of this medication is tardive dyskinesia, which can be irreversible. Erythromycin stimulates both cholinergic and motilin receptors, but because tachyphylaxis occurs with long-term use, it is most often used transiently in hospitalized patients.

KEY FACTS

✓ Risk of PUD increases with higher NSAID doses or with use of ≥2 NSAIDs

✓ Greatest risk of PUD from NSAIDs—during the first month of use, in elderly patients, and in patients with a previous history of PUD

✓ Diagnostic testing for gastroparesis—4-hour gastric scintigraphic study with a solid meal (after stopping opioids and after upper endoscopy to rule out mechanical obstruction)

Dumping Syndrome

Patients who have had prior resection of the gastric antrum and pylorus may be predisposed to *dumping syndrome*, which results from hyperosmolar substances rapidly exiting the stomach into the small bowel. Patients may report postprandial diarrhea, bloating, sweating, palpitations, and light-headedness. Symptoms can occur within 30 minutes after a meal (*early dumping*) or 1 to 3 hours after a meal (*late dumping*), which is associated with hypoglycemia and neuroglycopenic symptoms. Management includes having patients avoid hyperosmolar nutrient drinks, which aggravate symptoms; patients can modify their diets to include foods that delay gastric emptying (fats and proteins).

22

Liver and Biliary Disorders[a]

WILLIAM SANCHEZ, MD

Liver Testing

Commonly Used Liver Tests

Aminotransferases

Aminotransferases are found in hepatocytes and "leak" out of liver cells within a few hours after liver cell injury. The aminotransferases are alanine aminotransferase (ALT) and aspartate aminotransferase (AST). ALT is more specific than AST for liver injury; however, markedly increased levels of muscle enzymes may also be associated with increases in both AST and ALT. Because ALT has a longer half-life, improvements in ALT lag behind improvements in AST.

Alkaline Phosphatase

Alkaline phosphatase (ALP) is found not only in hepatocytes but also in bone and placenta; thus, an isolated increase in serum ALP should prompt further testing to determine the origin of the enzyme. This can be done either by determining ALP isoenzyme levels or by determining the level of γ-glutamyltransferase (GGT), a more specific hepatic enzyme. Other than to confirm the hepatic origin of an increased ALP level, GGT has little role in the diagnosis of diseases of the liver because its synthesis can be induced by many medications, which decreases its specificity for clinically important liver disease.

Bilirubin

Indirect (unconjugated) bilirubin, the water-insoluble product of heme metabolism, is taken up by the hepatocyte and conjugated to make water-soluble direct bilirubin, which can then be excreted in the bile. Overproduction of bilirubin, such as during hemolysis or resorption of a hematoma, is characterized by indirect hyperbilirubinemia (<20% conjugated [direct] bilirubin). Hepatocyte dysfunction or impaired bile flow usually causes direct hyperbilirubinemia (usually >50% conjugated bilirubin). Because conjugated bilirubin is water soluble it may be excreted in the urine, which results in darker urine; consequently, a lack of bilirubin pigments in the stool results in lighter stools.

Prothrombin Time and Albumin

Prothrombin time (PT), expressed as the international normalized ratio (INR), and serum albumin are markers of liver synthetic function. INR is a measure of the activity of coagulation factors II, V, VII, and X, which are synthesized in the liver. Because these factors are dependent on vitamin K for synthesis, vitamin K deficiency can also prolong INR. Vitamin K deficiency can result from antibiotic use associated with fasting, small-bowel mucosal disorders such as celiac disease, and severe cholestasis, with an inability to absorb fat-soluble vitamins. A simple way to distinguish between vitamin K deficiency and liver dysfunction in a patient with a prolonged PT is to administer a 10-mg dose of oral vitamin K for 3 days or 10 mg of subcutaneous vitamin K. Vitamin K normalizes the PT within 48 hours in a vitamin K–deficient patient, but it has no effect on the PT in a patient with decreased liver synthetic function.

Because albumin has a half-life of 21 days, serum albumin does not decrease suddenly with liver dysfunction. However, serum albumin can decrease quickly with severe systemic illness such as bacteremia, most likely from accelerated metabolism of albumin. A chronic decrease of albumin in a patient without liver disease should prompt a search for albumin in the urine.

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[a] Portions previously published in Poterucha JJ. Hepatitis. In: Bland KI, Büchler MW, Csendes A, Garden OJ, Sarr MG, Wong J, editors. General surgery: principles and international practice. 2nd ed. Vol 1. London (UK): Springer-Verlag; c2009. p. 921-32; used with permission.

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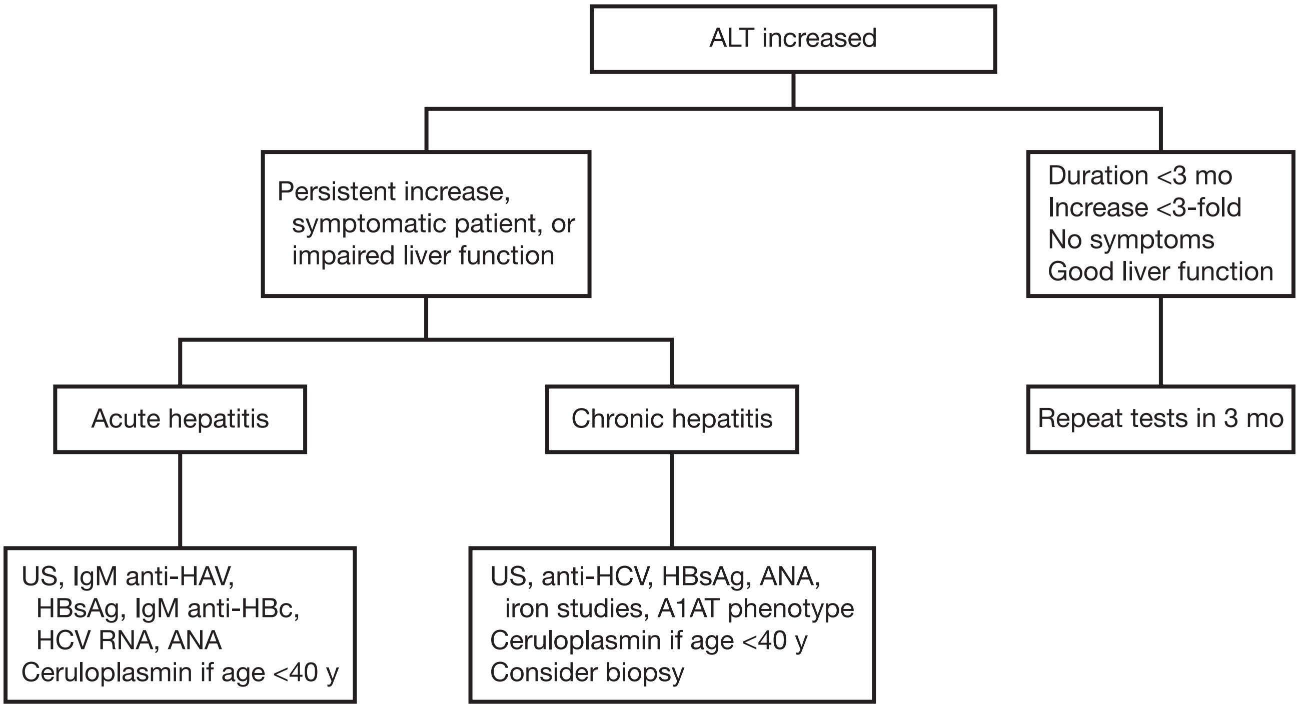
ALT increased
Persistent increase, symptomatic patient, or impaired liver function
Duration <3 mo
Increase <3-fold
No symptoms
Good liver function
Acute hepatitis
Chronic hepatitis
Repeat tests in 3 mo
US, IgM anti-HAV, HBsAg, IgM anti-HBc, HCV RNA, ANA
Ceruloplasmin if age <40 y
US, anti-HCV, HBsAg, ANA, iron studies, A1AT phenotype
Ceruloplasmin if age <40 y
Consider biopsy

Figure 22.1. *Evaluation of Increased Levels of Alanine Aminotransferase (ALT). A1AT indicates* α_1*-antitrypsin; ANA, antinuclear antibody; anti-HAV, hepatitis A virus antibody; anti-HBc, antibody to hepatitis B core antigen; anti-HCV, hepatitis C virus antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; IgM, immunoglobulin M; US, ultrasonography.*

(Modified from Poterucha JJ. Approach to the patient with abnormal liver tests and fulminant liver failure. In: Hauser SC, editor. Mayo Clinic gastroenterology and hepatology board review. 3rd ed. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2008. p. 283-92; used with permission of Mayo Foundation for Medical Education and Research.)

Abnormal Liver Test Results

The evaluation of patients who have abnormal liver test results includes many clinical factors: the patient's symptoms, age, risk factors for liver disease, personal or family history of liver disease, medications, and physical examination findings. A standard algorithm can aid in evaluating abnormal liver test results in an efficient, cost-effective manner.

The patient's clinical presentation should also be considered when interpreting abnormal results. In general, patients with abnormal liver test results that are less than 3 times the normal value can be observed unless the patient is symptomatic or the albumin level, INR, or bilirubin concentration is abnormal. Persistent abnormalities should be evaluated. Algorithms for case management in patients with increased ALT or ALP levels are shown in Figures 22.1 and 22.2, respectively.

Hepatocellular Disorders

Hepatocellular disorders primarily affect hepatocytes and are characterized predominantly by increases in aminotransferase levels. The disorders are best considered as acute (generally <3 months) or chronic. Common causes of marked acute increases in ALT are listed in Table 22.1.

Acute hepatitis may be accompanied by malaise, anorexia, abdominal pain, and jaundice. Acute hepatitis due to viruses or drugs generally produces markedly increased aminotransferase levels (which are often thousands of units per liter); generally, ALT is higher than AST. An ALT concentration greater than 5,000 U/L is usually caused by acetaminophen hepatotoxicity, hepatic ischemia (shock liver), or unusual viruses such as herpes simplex virus. Hepatic ischemia typically occurs in patients with preexisting heart disease after an episode of hypotension. Aminotransferase levels are very high but decrease considerably within a few days. Transient bile duct obstruction, usually from a stone, can also cause increases in aminotransferase levels as high as 1,000 U/L, but they decrease within 24 to 48 hours. Pancreatitis with a transient increase in AST or ALT concentration suggests gallstone pancreatitis. Alcoholic hepatitis is characterized by more modest increases in aminotransferases (always <400 U/L and, at times, near the reference range) with an AST:ALT ratio greater than 2. Patients with alcoholic hepatitis often have a bilirubin level that is markedly increased out of proportion to the aminotransferase increases.

Diseases that produce a sustained (>3 months) increase in aminotransferase levels are in the category of *chronic hepatitis*. The increase (usually 2-fold to 5-fold) in aminotransferase levels is more modest than in acute hepatitis. Patients are usually asymptomatic

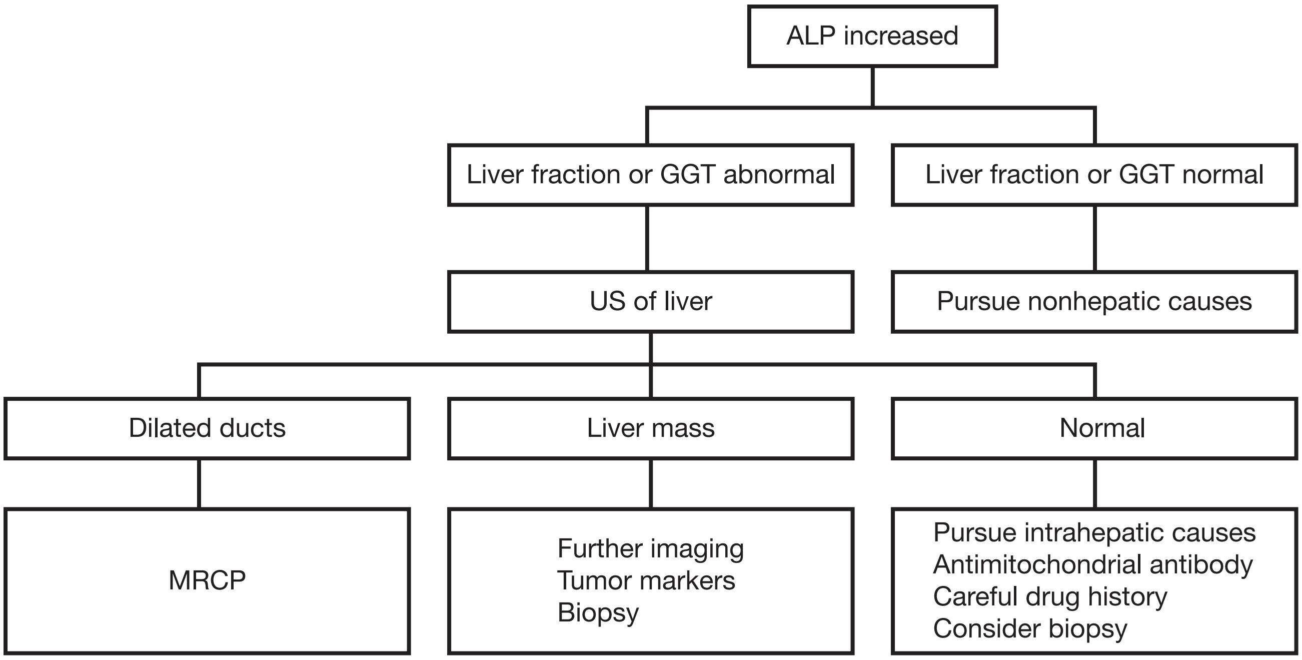
ALP increased
Liver fraction or GGT abnormal
Liver fraction or GGT normal
US of liver
Pursue nonhepatic causes
Dilated ducts
Liver mass
Normal
MRCP
Further imaging
Tumor markers
Biopsy
Pursue intrahepatic causes
Antimitochondrial antibody
Careful drug history
Consider biopsy

Figure 22.2. *Evaluation of Increased Levels of Alkaline Phosphatase (ALP). GGT indicates γ-glutamyltransferase; MRCP, magnetic resonance cholangiopancreatography; US, ultrasonography.*

(Modified from Poterucha JJ. Approach to the patient with abnormal liver tests and fulminant liver failure. In: Hauser SC, editor. Mayo Clinic gastroenterology and hepatology board review. 3rd ed. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2008. p. 283-92; used with permission of Mayo Foundation for Medical Education and Research.)

but occasionally report fatigue and right upper quadrant pain. The differential diagnosis of chronic hepatitis is relatively lengthy; the more important and common causes are listed in Table 22.2.

Table 22.1 • Common Causes of a Marked Acute Increase in ALT

Disease	Clinical Clue	Diagnostic Test
Hepatitis A	Exposure history	IgM anti-HAV
Hepatitis B	Risk factors	HBsAg IgM anti-HBc
Drug-induced hepatitis	Compatible medication or timing	Improvement after withdrawal of the agent
Alcoholic hepatitis	History of alcohol excess AST:ALT >2 AST <400 U/L	Clinical improvement with abstinence
Hepatic ischemia	History of hypotension and heart disease	Rapid improvement of aminotransferase levels
Acute biliary obstruction	Abdominal pain Fever ALT >3× reference range (specificity >95%, low sensitivity)	Cholangiography

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HAV, hepatitis A virus; anti-HBc, antibody to hepatitis B core antigen; HBsAg, hepatitis B surface antigen; Ig, immunoglobulin.

KEY FACTS

✓ ALT—more specific than AST for liver injury (increased muscle enzyme levels may be associated with increased AST and ALT)

✓ Vitamin K deficiency—giving vitamin K normalizes the PT within 48 hours unless the patient has decreased liver synthetic function

✓ ALT >5,000 U/L—usually caused by acetaminophen hepatotoxicity, hepatic ischemia, or unusual viruses

✓ Transient increase in AST or ALT in a patient with pancreatitis suggests gallstone pancreatitis

✓ Alcoholic hepatitis—

- modestly increased aminotransferases (<400 U/L and sometimes nearly normal)
- AST:ALT ratio >2
- bilirubin increased out of proportion to aminotransferase increases

Table 22.2 • Common Causes of Chronic Hepatitis

Disease	Clinical Clue	Diagnostic Test
Hepatitis C	Risk factors	Anti-HCV HCV RNA
Hepatitis B	Risk factors	HBsAg
Nonalcoholic steatohepatitis	Obesity Diabetes mellitus Hyperlipidemia	Steatosis on liver imaging, liver biopsy
Alcoholic liver disease	History AST:ALT >2	Clinical liver biopsy
Autoimmune hepatitis	ALT 200-1,500 U/L Usually female Other autoimmune disease	Strongly positive antinuclear or anti–smooth muscle antibody (or both) Hypergammaglobulinemia Liver biopsy

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

Cholestatic Disorders

Diseases that predominantly affect the biliary system are called cholestatic diseases. They can affect the microscopic ducts (eg, primary biliary cholangitis) or the large bile ducts (eg, pancreatic cancer causing obstruction of the common bile duct), or both (eg, primary sclerosing cholangitis). Generally, the predominant laboratory abnormality in these disorders is the ALP level. Although diseases that increase the bilirubin level are often referred to as cholestatic, severe hepatocellular injury (as in acute hepatitis) also produces hyperbilirubinemia because of hepatocellular dysfunction. The common causes of cholestasis are listed in Table 22.3.

Table 22.3 • Common Causes of Cholestasis

Disease	Clinical Clue	Diagnostic Test
Primary biliary cholangitis	Middle-aged woman	Antimitochondrial antibody
Primary sclerosing cholangitis	Association with ulcerative colitis	Cholangiography (ERCP or MRCP)
Large bile duct obstruction	Jaundice or pain (or both)	Ultrasonography, ERCP, or MRCP
Drug-induced cholestasis	Compatible medication or timing	Improvement after withdrawal of the agent
Infiltrative disorder or cancer	Other clinical features of cancer, sarcoidosis, or amyloidosis	Ultrasonography Computed tomography Liver biopsy
Inflammation-associated cholestasis	Symptoms of underlying inflammatory state	Blood cultures Appropriate antibody tests

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography.

Jaundice

Jaundice is visibly evident hyperbilirubinemia, which occurs when the serum bilirubin concentration exceeds approximately 2.5 mg/dL. Evaluation of a patient with jaundice is an important diagnostic skill (Figure 22.3). Conjugated hyperbilirubinemia must be distinguished from unconjugated hyperbilirubinemia. A common disorder that produces unconjugated hyperbilirubinemia is Gilbert syndrome, in which total bilirubin is generally less than 3.0 mg/dL and direct bilirubin is 0.3 mg/dL or less; the concentration of bilirubin is generally higher in the fasting state or in illness. A presumptive diagnosis of Gilbert syndrome can be made when an otherwise well person has unconjugated hyperbilirubinemia, normal hemoglobin levels (which excludes hemolysis), and normal liver enzyme values (which excludes liver disease).

Key Definition

Jaundice: *visibly evident hyperbilirubinemia.*

Conjugated hyperbilirubinemia is a more common cause of jaundice than unconjugated hyperbilirubinemia. Patients with conjugated hyperbilirubinemia can be categorized as having nonobstructive conditions or obstructive conditions. The presence of risk factors for viral hepatitis, a bilirubin concentration greater than 15 mg/dL, and persistently high aminotransferase values suggest that the jaundice is from hepatocellular dysfunction. Abdominal pain, fever, or a palpable gallbladder (or a combination of these) suggests obstruction.

A sensitive, specific, and noninvasive test to exclude obstructive causes of cholestasis is hepatic ultrasonography. With diseases characterized by obstruction of a large bile duct, ultrasonography generally shows intrahepatic bile duct dilatation, especially if the bilirubin concentration is greater than 10 mg/dL and the patient has had jaundice for more than 2 weeks. Acute obstruction of a large bile duct, usually from a stone, may not allow time for the bile ducts to dilate. An important clue to the presence of an acute large-duct obstruction is a marked but transient increase in aminotransferase levels. If clinical suspicion for obstruction of the bile duct is still strong despite negative ultrasonographic results, magnetic resonance cholangiography should be considered. Uncomplicated gallbladder disease, such as cholelithiasis with or without cholecystitis, does not cause jaundice or abnormal liver test results unless a common bile duct stone or sepsis is present.

Specific Liver Diseases

Viral Hepatitis

Hepatitis A

Owing to vaccination and improvements in food handling, hepatitis A virus (HAV) infection is becoming an unusual cause of acute hepatitis in the United States. The disease generally is transmitted by the fecal-oral route and has an

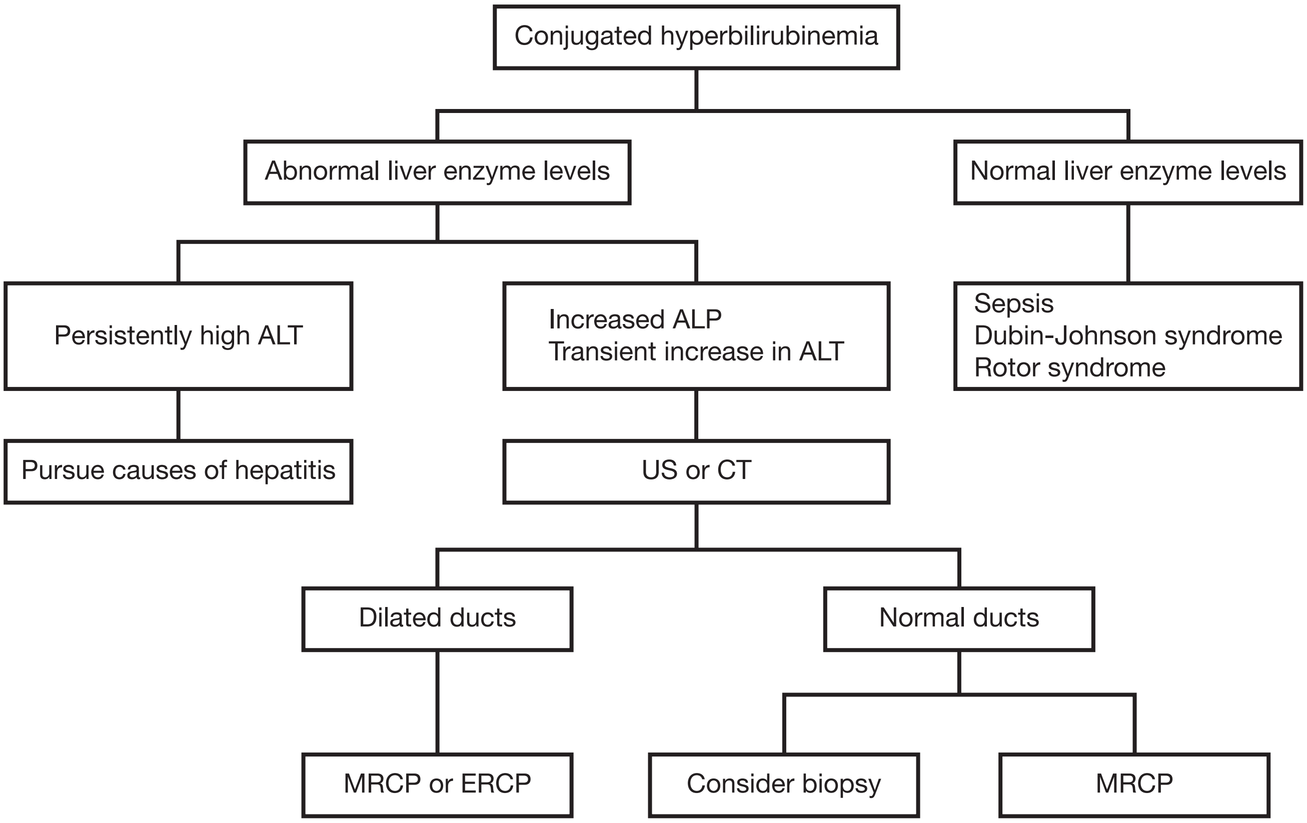

Figure 22.3. *Evaluation of Conjugated Hyperbilirubinemia. ALP indicates alkaline phosphatase; ALT, alanine aminotransferase; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography; US, ultrasonography.*

(Modified from Poterucha JJ. Approach to the patient with abnormal liver tests and fulminant liver failure. In: Hauser SC, editor. Mayo Clinic gastroenterology and hepatology board review. 3rd ed. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2008. p. 283-92; used with permission of Mayo Foundation for Medical Education and Research.)

incubation period of 15 to 50 days. Major routes of transmission of HAV are ingestion of contaminated food or water and contact with an infected person. Persons at highest risk for HAV infection are those living in or traveling to developing countries, children in daycare centers, and men who have sex with men. Hepatitis caused by HAV is generally mild in children, who often have a subclinical or nonicteric illness. Infected adults are more ill and are usually icteric. The prognosis is excellent, although HAV can rarely cause acute liver failure. Chronic liver disease does not develop from HAV. Serum immunoglobulin (Ig) M anti-HAV is present during an acute illness and generally persists for 2 to 6 months. IgG anti-HAV appears slightly later, persists for life, and offers immunity from further infection.

Hepatitis B

Hepatitis B virus (HBV) is a DNA virus that is transmitted by exposure to blood or contaminated body fluids. In high-prevalence areas (eg, certain areas of Asia and Africa), HBV is acquired perinatally. High-risk groups in the United States include persons born in an area where HBV is endemic, injection drug users, and persons with multiple sexual contacts.

The clinical course of HBV infection varies. Symptoms of acute hepatitis (when present) are similar but generally more severe than those in HAV infection. Most acute infections in adults are subclinical, and even when symptomatic, the disease resolves within 6 months with subsequent development of immunity. However, more than 90% of those infected as neonates do not clear hepatitis B surface antigen (HBsAg) from the serum within 6 months and, thus, become chronically infected. These patients usually go through an immune-tolerant phase, characterized by normal ALT levels, positive hepatitis B e antigen (HBeAg), very high HBV DNA levels, and no fibrosis on liver biopsy. Treatment is not recommended. The natural history of chronic infection is illustrated in Figure 22.4.

The immune-tolerant phase evolves under immune pressure into the HBeAg-positive chronic hepatitis B phase, characterized by increased ALT levels, the presence of HBeAg, high HBV DNA levels, and active inflammation and often fibrosis on liver biopsy. This phase leads to progressive liver damage,

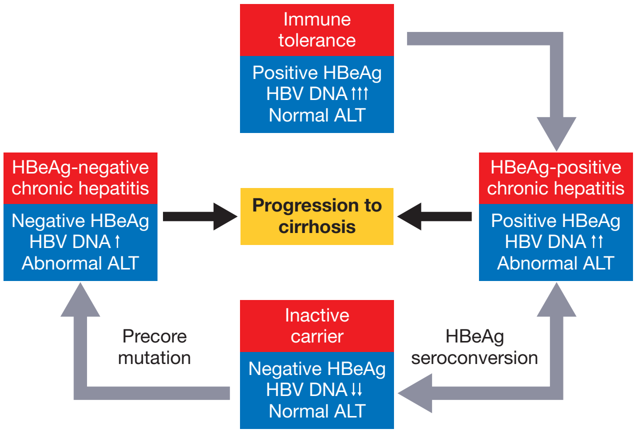

Figure 22.4. Phases of Chronic Hepatitis B Virus (HBV) Infection. Black arrows represent histopathologic changes; gray arrows represent changes in serologic markers between phases; thin arrows represent an increase or decrease in DNA level (↑, small increase; ↑↑, moderate increase; ↓↓, moderate decrease; ↑↑↑, large increase). ALT indicates alanine aminotransferase; HBeAg, hepatitis B e antigen.

(Modified from Pungpapong S, Kim WR, Poterucha JJ. Natural history of hepatitis B virus infection: an update for clinicians. Mayo Clin Proc. 2007 Aug;82[8]:967-75; used with permission of Mayo Foundation for Medical Education and Research.)

including cirrhosis and an increased risk of hepatocellular carcinoma (HCC). About 10% of patients per year become inactive carriers, a state characterized by a decrease in ALT levels, clearance of HBeAg, development of antibodies to hepatitis B e antigen (anti-HBe) (seroconversion), and a decrease in HBV DNA. This inactive carrier state is not associated with progressive liver damage. About 60% of patients with chronic hepatitis B are in the inactive carrier phase. About one-third of inactive carriers have a recurrence of chronic hepatitis (HBeAg positive or negative), which is characterized by abnormal ALT levels and increased HBV DNA levels and is associated with progression of liver disease.

Patients with chronic hepatitis B and cirrhosis are at high risk for HCC, and liver ultrasonography should be performed every 6 to 12 months, especially for Asian men older than 40 years, Asian women older than 50 years, African persons older than 20 years, patients with a family history of HCC, and patients with persistent increases in ALT and HBV DNA.

Patients with chronic hepatitis B, an abnormal ALT level, and high HBV DNA are candidates for therapy. Treatment options are compared and contrasted in Table 22.4. Treatment response is measured by the loss of HBeAg, the suppression of HBV DNA, and the appearance of anti-HBe (rarely, the loss of HBsAg). Peginterferon injection is considered for those with high serum aminotransferase levels, active hepatitis without evidence of cirrhosis on biopsy, and low serum levels of HBV DNA. Oral drugs have fewer adverse effects and are safer than peginterferon for patients with cirrhosis because flares of hepatitis and infectious complications are uncommon. Resistance is a concern with the oral agents, but entecavir and tenofovir have lower resistance rates and, thus, are the preferred oral drugs for treatment.

A brief guide to the interpretation of serologic markers of hepatitis B is shown in Table 22.5. Viral markers in the blood during a self-limited infection with HBV are shown in Figure 22.5. Note that IgM antibodies to hepatitis B core antigen (anti-HBc) are nearly always present during acute hepatitis B.

Hepatitis B immune globulin should be given to household and sexual contacts of patients with acute hepatitis B. Infants should receive HBV vaccine. The marker of immunity is hepatitis B surface antibodies (anti-HBs). Because infected neonates are at high risk for chronic infection, all pregnant women should be tested for HBsAg. If a pregnant woman is HBsAg-positive, the infant should receive both hepatitis B immune globulin and HBV vaccine. Some pregnant women with very high HBV DNA levels may be advised to undergo treatment with lamivudine or tenofovir during the third trimester. Patients who are HBsAg-positive and are receiving immunosuppressive therapy should also receive hepatitis B treatment to prevent a flare of disease activity, even if they do not meet the other recommendations for therapy.

Table 22.4 • Agents for Treatment of Hepatitis B Virus Infection

Feature	**Peginterferon**	**Lamivudine**	**Adefovir**	**Entecavir**	**Telbivudine**	**Tenofovir**
Treatment duration	12 mo	Indefinite	Indefinite	Indefinite	Indefinite	Indefinite
Adverse effects	Many	Minimal	Rarely renal	Minimal	Minimal	Minimal
Disease flare	Common	Rare	Rare	Rare	Rare	Rare
HBeAg seroconversion, %	27	20	12	21	22	20
Resistance	None	12%-15% yearly	1%-4% yearly	1%-2% yearly	22% at 2 y	None

Abbreviation: HBeAg, hepatitis B e antigen.

Table 22.5 • Hepatitis B Serologic Markers

Test	Interpretation of Positive Results
Hepatitis B surface antigen (HBsAg)	Current infection
Antibody to hepatitis B surface (anti-HBs)	Immunity (immunization or resolved infection)
IgM antibody to hepatitis B core (IgM anti-HBc)	Usually recent infection; occasionally "reactivation" of chronic infection
IgG antibody to hepatitis B core (IgG anti-HBc)	Remote infection
Hepatitis B e antigen (HBeAg) or HBV DNA >10^4 IU/mL	Active viral replication
Antibody to hepatitis B e (anti-HBe)	Remote infection

Abbreviations: HBV, hepatitis B virus; Ig, immunoglobulin.

Modified from Poterucha JJ. Viral hepatitis. In: Hauser SC, editor. Mayo Clinic gastroenterology and hepatology board review. 5th ed. Rochester (MN): Mayo Clinic Scientific Press and New York (NY): Oxford University Press; c2015. p. 244-51; used with permission of Mayo Foundation for Medical Education and Research.

KEY FACTS

- ✓ Presumptive diagnosis of Gilbert syndrome—
    - patient is well otherwise
    - unconjugated hyperbilirubinemia
    - normal hemoglobin level
    - normal liver enzyme levels
- ✓ Hepatic ultrasonography—sensitive, specific, and noninvasive test for excluding obstructive causes of cholestasis
- ✓ HAV transmission—ingestion of contaminated food or water; contact with infected person
- ✓ HAV does not cause chronic liver disease
- ✓ Patients with chronic hepatitis B and cirrhosis—high risk for HCC (liver ultrasonography every 6-12 months for monitoring)
- ✓ Patients with chronic hepatitis B, abnormal ALT level, and high HBV DNA level should receive therapy

Hepatitis D

Hepatitis D virus (HDV), or delta agent, is a small RNA particle that requires the presence of HBsAg to cause infection. HDV infection can occur simultaneously with acute HBV infection (coinfection), or HDV may infect a patient with chronic hepatitis B (superinfection). Infection with HDV should be considered only for patients with HBsAg; diagnosis is based on HDV antibody seroconversion.

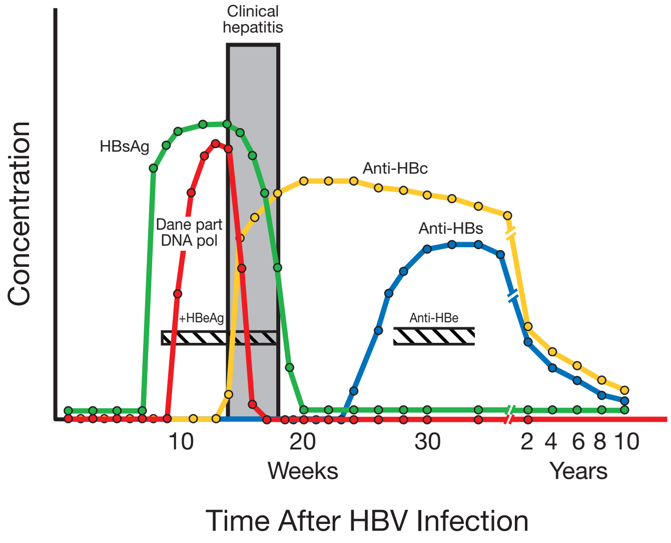

Figure 22.5. *Viral Markers in Blood During Self-limited Hepatitis B Virus (HBV) Infection. Anti-HBc indicates hepatitis B core antibody; anti-HBe, hepatitis B e antibody; anti-HBs, hepatitis B surface antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; part, particle; pol, polymerase.*

(Modified from Robinson WS. Biology of human hepatitis viruses. In: Zakim D, Boyer TD, editors. Hepatology: a textbook of liver disease. Vol 2. 2nd ed. Philadelphia [PA]: WB Saunders Company; c1990. p. 890-945; used with permission.)

Hepatitis C

Hepatitis C virus (HCV), an RNA virus, is the most common cause of chronic bloodborne infection in the United States. HCV has a role in 40% of all cases of chronic liver disease, and cirrhosis due to HCV infection is the most common indication for liver transplant. The most common risk factor is illicit drug use. Persons with a history of transfusion of blood products before 1992 (the year routine testing of blood products for HCV was introduced) are also at considerable risk for infection with HCV. Sexual transmission of HCV occurs but seems to be inefficient. The risk of transmission of HCV to health care workers by percutaneous (needlestick) exposure is also low—approximately 2% for a needlestick exposure to an infected patient.

Patients with HCV infection rarely have acute hepatitis. The natural history of hepatitis C is summarized in Figure 22.6. In about 60% to 85% of persons who acquire HCV, a chronic infection develops; after chronic infection is established, subsequent spontaneous loss of the virus is rare. Consequently, in most patients, HCV infection presents as chronic hepatitis with mild to moderate increases in ALT levels. Some patients have fatigue or vague right upper quadrant pain. Patients may also receive medical attention because of complications of end-stage liver disease or, rarely, extrahepatic complications such as cryoglobulinemia or porphyria cutanea tarda. Because most patients

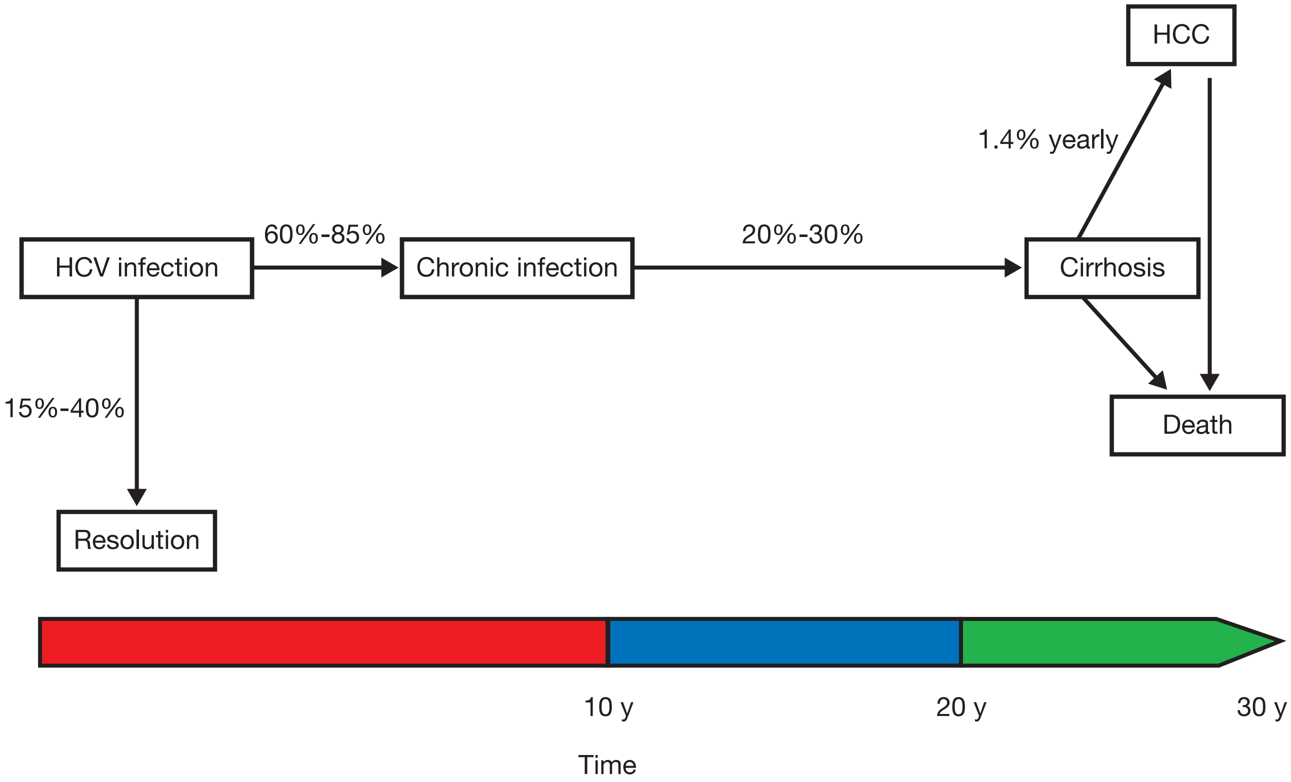

Figure 22.6. *Natural History of HCV Infection. Values are percentages of patients. HCC indicates hepatocellular carcinoma.* (Modified from Poterucha JJ. Viral hepatitis. In: Hauser SC, editor. Mayo Clinic gastroenterology and hepatology board review. 5th ed. Rochester [MN]: Mayo Clinic Scientific Press and New York [NY]: Oxford University Press; c2015. p. 244-51; used with permission of Mayo Foundation for Medical Education and Research.)

with hepatitis C are asymptomatic, treatment is generally aimed at preventing future complications of the disease. Patients with cirrhosis due to HCV generally have had HCV infection for more than 20 years.

Antibodies to HCV (anti-HCV) indicate exposure to the virus (current infection or previous infection with subsequent clearance) and are not protective. The presence of anti-HCV in a patient with abnormal ALT values and risk factors for hepatitis C is strongly suggestive of current HCV infection. Initial detection of anti-HCV is with enzyme-linked immunosorbent assay (ELISA). HCV infection is diagnosed by determining the presence of HCV RNA (Table 22.6). Levels of HCV RNA do not correlate with disease severity and are mainly used to assess response to therapy. Similarly, HCV genotypes do not affect disease severity but do affect drug selection and treatment response. Most patients in the United States are infected with HCV genotype 1.

All patients with hepatitis C should be counseled on preventing liver damage, most notably through avoidance of alcohol. Therapy for hepatitis C has changed drastically in the recent past. Previously, peginterferon-based combination therapy required prolonged treatment (often 48 weeks) and was associated with a high rate of adverse effects; a sustained virologic response was achieved in less than 70% of treated patients. With the advent of potent, orally administered, direct-acting antiviral (DAA) agents, patients can now be treated with shorter courses (8-12 weeks) of oral medications, with very low rates of adverse effects and sustained virologic response rates of more than 95%. Patients who do not respond

Table 22.6 • Interpretation of Anti-HCV Results

Anti-HCV by ELISA	Anti-HCV by RIBA	Interpretation
Positive	Negative	False-positive ELISA Patient does not have true antibody
Positive	Positive	Patient has antibody[a]
Positive	Indeterminate	Uncertain antibody status

Abbreviations: ELISA, enzyme-linked immunosorbent assay; anti-HCV, antibodies to hepatitis C virus; RIBA, recombinant immunoblot assay.

[a] Anti-HCV does not necessarily indicate current hepatitis C infection (see text).

to or do not tolerate peginterferon-based therapy typically are successfully treated with DAA agents. Treatment of hepatitis C continues to evolve. Multiple new agents have become available recently, and new agents will most likely continue to enter practice in the near future. DAA treatment programs contain combinations of various classes of antiviral drugs (eg, protease inhibitors, polymerase inhibitors, and HCV NS5A protein inhibitors). The selection of DAA agent depends in part on the HCV genotype, although newer DAA regimens are effective against all genotypes (pangenotypic efficacy).

The risk of HCC complicating hepatitis C with cirrhosis is 1% to 4% per year. Surveillance with liver imaging every 6 months is advised for patients who are potential candidates for treatment with liver transplant, percutaneous ablation, transarterial chemoembolization, or radioembolization. Patients with HCV infection and decompensated cirrhosis should be considered for liver transplant.

Hepatitis E

Hepatitis E virus is an enterically transmitted RNA virus that causes acute hepatitis primarily in patients who have lived or traveled in areas where the virus is endemic (India, Pakistan, Mexico, and Southeast Asia); however, hepatitis E is increasingly diagnosed in patients who have not visited those areas. Clinically, hepatitis E resembles hepatitis A.

Other Viral Causes of Hepatitis

Epstein-Barr virus, cytomegalovirus, and herpesvirus may all cause hepatitis as part of a clinical syndrome. Infections with these agents are most serious in immunocompromised patients. Immunocompetent patients with infectious mononucleosis syndromes commonly have abnormal liver test results and mild increases in bilirubin, although clinically recognized jaundice is unusual. Herpes hepatitis generally occurs in immunosuppressed or pregnant patients and is characterized by fever, mental status changes, absence of jaundice, and AST and ALT values greater than 5,000 U/L.

Autoimmune Hepatitis

Autoimmune hepatitis was previously called "autoimmune chronic active hepatitis" because the diagnosis required 3 to 6 months of abnormal liver enzyme test results. However, in 40% of patients autoimmune hepatitis presents as clinical acute hepatitis. Autoimmune hepatitis can affect patients of any age, predominantly females. By definition, patients with autoimmune hepatitis should not have a history of drug-related hepatitis, HBV or HCV infection, or Wilson disease. Immunoserologic markers, such as antinuclear antibody (ANA), smooth muscle antibody, soluble liver antigen antibodies, or antibodies to liver-kidney microsomal antigens, are usually detected. Patients with autoimmune hepatitis may have other autoimmune diseases, including Hashimoto thyroiditis. Aminotransferase levels are generally 4 to 20 times the reference range, and most patients have increased gamma globulin levels. Corticosteroids (30-60 mg daily) produce improvement in most patients, with often marked improvements in liver test results and gamma globulin levels. The addition of azathioprine allows for the use of lower doses of prednisone. Immunosuppressive doses should be decreased to control symptoms and to maintain the serum aminotransferase values to less than 5 times the reference range. Even after an excellent response to corticosteroids, relapse often occurs and the control of autoimmune hepatitis usually requires maintenance therapy.

KEY FACTS

✓ Hepatitis D—
- HDV requires HBsAg to replicate
- HDV can be transmitted with HBV (coinfection)
- can develop in patients with chronic hepatitis B (superinfection)

✓ Major risk factors for acquiring HCV infection—
- injection drug use
- received transfusion of blood products before 1992

✓ Hepatitis C—rarely acute; usually HCV infection is chronic

✓ Treatment of hepatitis C—new DAA agents provide sustained virologic response rates >90% for most patients

✓ Autoimmune hepatitis—usually serum autoantibodies are present (eg, ANA and smooth muscle antibody) and IgG levels are increased

✓ Autoimmune hepatitis therapy—
- corticosteroids help most patients
- other immunosuppressants (eg, azathioprine) are used as steroid-sparing agents for maintenance therapy

Alcoholic Liver Disease

Alcoholic Hepatitis

Long-term, excessive use of alcohol (>20 g daily for women and >40 g daily for men) can produce advanced liver disease. Alcoholic hepatitis is characterized histologically by fatty change, degeneration and necrosis of hepatocytes (with or without Mallory bodies), and an inflammatory infiltrate of neutrophils. Almost all patients have fibrosis, and they may have cirrhosis. Clinically, patients with alcoholic hepatitis may be asymptomatic or icteric and critically ill. Common symptoms include anorexia, nausea, vomiting, abdominal pain, and weight loss. The most common sign is hepatomegaly, which may be accompanied by ascites, jaundice, fever, splenomegaly, and encephalopathy. The AST level is increased in 80% to 90% of patients, but it is almost always less than 400 U/L. The AST:ALT ratio is frequently greater than 2. Leukocytosis is commonly present, particularly in severely ill patients. Although the constellation of symptoms may mimic biliary disease, the clinical features are characteristic in an alcoholic patient. Because cholecystectomy carries a substantial risk of morbidity among patients with alcoholic hepatitis, the clinical distinction is important.

Markers of poor prognosis in alcoholic hepatitis include encephalopathy, spider angiomas, ascites, renal failure, prolonged PT, and a bilirubin concentration greater than 20 mg/dL. Many patients have disease progression, particularly if alcohol intake is not curtailed. Corticosteroid therapy may be beneficial as an acute treatment of alcoholic hepatitis in patients with severe disease characterized by encephalopathy and a markedly prolonged PT. A *discriminant function* (DF) greater than 32 helps to identify patients with a poor prognosis:

$$\mathrm{DF} = 4.6(\mathrm{PT}_{\text{patient}} - \mathrm{PT}_{\text{control}}) + \text{Bilirubin (mg / dL)}.$$

Alcoholic Cirrhosis

Cirrhosis is defined histologically by septal fibrosis with nodular parenchymal regeneration. Only 60% of patients with alcoholic cirrhosis have signs or symptoms of liver disease, and most patients with alcoholic cirrhosis lack a clinical history of alcoholic hepatitis. Liver enzyme levels may be relatively normal in patients who have cirrhosis without alcoholic hepatitis. The prognosis for patients with alcoholic cirrhosis depends on whether they continue to consume alcohol and whether they have signs of chronic liver disease (jaundice, ascites, or gastrointestinal tract bleeding). For patients who do not have ascites, jaundice, or variceal bleeding and who abstain from alcohol, the 5-year survival rate is 89%; for patients who have any of those complications and continue to consume alcohol, it is 34%. Liver transplant is an option for patients with end-stage alcoholic liver disease if they show that they can maintain abstinence from alcohol. The outcome of liver transplant for alcoholic liver disease is similar to that of transplant for other indications.

Key Definition

Cirrhosis: *septal fibrosis with nodular parenchymal regeneration.*

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome and a common cause of abnormal liver enzyme values. Given the obesity epidemic in the United States, NAFLD has become increasingly common, even among children and adolescents. NAFLD is a spectrum of disorders ranging from simple fatty infiltration (steatosis) to nonalcoholic steatohepatitis (NASH), which is characterized histologically by fatty change, inflammation, and progressive fibrosis. Characteristically, patients with NAFLD have at least 1 of the following risk factors: central obesity, hypertension, hyperlipidemia, and diabetes mellitus. The aminotransferase levels are mildly abnormal, and ALP levels are increased in about one-third of patients. When advanced cirrhosis develops, fat may no longer be recognizable in liver tissue, and NASH most likely accounts for some cases of "cryptogenic" cirrhosis. In 10% of patients, NAFLD progresses to cirrhosis. The risk factors for more advanced disease are older age, marked obesity, and diabetes mellitus. Other than to control risk factors, there is no approved therapy for NAFLD. When patients have fat in the liver, other diseases that result in steatosis must be ruled out, including hepatitis C, celiac disease, Wilson disease, and alcoholic liver disease.

Aggressive treatment of obesity, hyperlipidemia, and diabetes mellitus is indicated for patients with NAFLD. The weight loss that occurs after bariatric surgery improves the histologic features of NAFLD. Vitamin E has been shown to improve liver test results and histologic features in patients with NAFLD. Use of agents such as pioglitazone and rosiglitazone has resulted in biochemical and histologic improvement but also in weight gain. For treatment of hyperlipidemia, the statin drugs are safe in patients with NAFLD. For patients with NAFLD who are given potentially hepatotoxic medications, liver enzymes should be monitored regularly, and the use of the medications can continue as long as liver enzyme values are less than 5-fold the reference value and liver function is preserved.

Chronic Cholestatic Liver Diseases

Primary Biliary Cholangitis

Primary biliary cirrhosis has recently been renamed "primary biliary cholangitis"—both to better reflect its pathogenesis and to recognize that most patients no longer have cirrhotic-stage disease at the time of diagnosis—without the need to change its acronym (PBC). PBC is a chronic, progressive, cholestatic liver disease that primarily affects middle-aged women. Its cause is unknown but appears to involve an immunologic disturbance resulting in small bile duct destruction. In many patients, the disease is identified by an asymptomatic increase in ALP value. Common early symptoms are pruritus and fatigue. Patients may have Hashimoto thyroiditis or sicca complex. Biochemical features include increased ALP and IgM levels. When PBC is advanced, the bilirubin concentration is high, the serum albumin level is low, and PT is prolonged. Steatorrhea may occur because of progressive cholestasis. Fat-soluble vitamin deficiencies and metabolic bone disease are common.

Antimitochondrial antibodies are present in 90% to 95% of patients with PBC. The classic histologic lesion is granulomatous infiltration of septal bile ducts. Ursodiol treatment benefits patients who have this disease by improving survival and delaying the need for liver transplant. Obeticholic acid has recently been approved as a treatment in select patients who do not respond to ursodiol. Cholestyramine and rifampin may be beneficial in the management of pruritus.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by obliterative inflammatory fibrosis of extrahepatic and intrahepatic bile ducts. An immune mechanism has been implicated, but the exact pathogenesis remains unknown. Patients may have an asymptomatic increase in ALP level or progressive fatigue, pruritus, and jaundice. Bacterial cholangitis may occur in patients who have dominant strictures or who have undergone invasive procedures. Cholangiography, with either endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP), establishes the diagnosis of PSC, showing short strictures of bile ducts with intervening segments of normal or slightly dilated ducts. This cholangiographic appearance may be mimicked by HIV-associated cholangiopathy (due to cytomegalovirus or *Cryptosporidium* infection), ischemic cholangiopathy after intra-arterial infusion of fluorodeoxyuridine, and IgG4-associated cholangitis.

Among patients with PSC, 70% have ulcerative colitis, which may antedate, accompany, or even follow the diagnosis of PSC. The treatment of ulcerative colitis has no effect on the development or clinical course of PSC. Patients with PSC are at higher risk for cholangiocarcinoma; its development may be manifested by rapid clinical deterioration, jaundice, weight loss, and abdominal pain. There is no effective medical therapy for PSC. Treatment of PSC is generally supportive, and many patients have progressive liver disease and ultimately require a liver transplant. Endoscopic balloon dilatation of bile duct strictures may offer palliation, especially in patients with recurrent cholangitis.

KEY FACTS

✓ Alcoholic liver disease—

- AST:ALT ratio typically 2:1
- AST and ALT values nearly always <400 U/L

✓ DF in alcoholic hepatitis—

- $DF = 4.6(PT_{patient} - PT_{control}) + \text{Bilirubin (mg/dL)}$
- identifies patients who have severe hepatitis and may benefit from corticosteroid therapy

✓ NAFLD—

- risk factors: obesity, hyperlipidemia, and diabetes mellitus
- treatment centers on aggressive control of risk factors

✓ NAFLD—in some patients, NASH develops and may progress to cirrhosis, end-stage liver disease, and HCC

✓ PBC—

- typical presentation: fatigue, pruritus, and increased ALP levels in a middle-aged woman
- serum antimitochondrial antibody is present in 90%-95% of patients
- treatment with ursodiol improves survival

✓ PSC—

- strong association with ulcerative colitis, but PSC severity does not correlate with ulcerative colitis activity
- diagnosis: cholangiography with either ERCP or MRCP
- risk factor for bile duct cancer (cholangiocarcinoma)
- treatment: supportive, but many patients require liver transplant

Hereditary Liver Diseases

Genetic Hemochromatosis

Genetic hemochromatosis is an autosomal recessively transmitted disorder characterized by iron overload. The physiologic defect appears to be inappropriately high absorption of iron from the gastrointestinal tract. The *HFE* gene for genetic hemochromatosis has been identified. In the general population, the heterozygote frequency is 10%. Only those who are homozygous manifest progressive iron accumulation.

Patients often have end-stage disease at initial evaluation, although increased screening sensitivity is aiding in earlier diagnosis. The peak incidence of clinical presentation is between ages 40 and 60 years. Iron overload is manifested more often and earlier in men than in women because women are protected by the iron losses of menstruation and pregnancy. Although hemochromatosis is now usually diagnosed from screening iron test results, clinical features include arthropathy, hepatomegaly, skin pigmentation, diabetes mellitus, cardiac dysfunction, and hypogonadism. Hemochromatosis should be considered in patients with symptoms or diseases such as arthritis, diabetes mellitus, cardiac arrhythmias, or sexual dysfunction.

Routine liver biochemistry studies generally show few abnormalities, and complications of portal hypertension are unusual. Transferrin saturation greater than 50% is the earliest biochemical iron abnormality in hemochromatosis. High serum ferritin levels indicate tissue iron overload in patients with hemochromatosis. Increased iron and ferritin levels may occur in other liver diseases, particularly advanced cirrhosis of any cause. Testing for mutations in the *HFE* gene is the standard method for diagnosing hemochromatosis. Of the patients with hemochromatosis, 80% to 90% are homozygous for the C282Y mutation. Heterozygotes for C282Y generally do not have the disease. Patients who are heterozygous for C282Y and heterozygous for the H63D mutation (compound heterozygosity) may have iron overload.

Liver biopsy in patients with abnormal iron tests is done only if patients are negative for C282Y or if there is concern about cirrhosis. The knowledge of cirrhosis is important because of the increased risk of HCC. Generally, hepatic iron levels in hemochromatosis are greater than 10,000 μg/g dry weight. A diagnostic algorithm is shown in Figure 22.7.

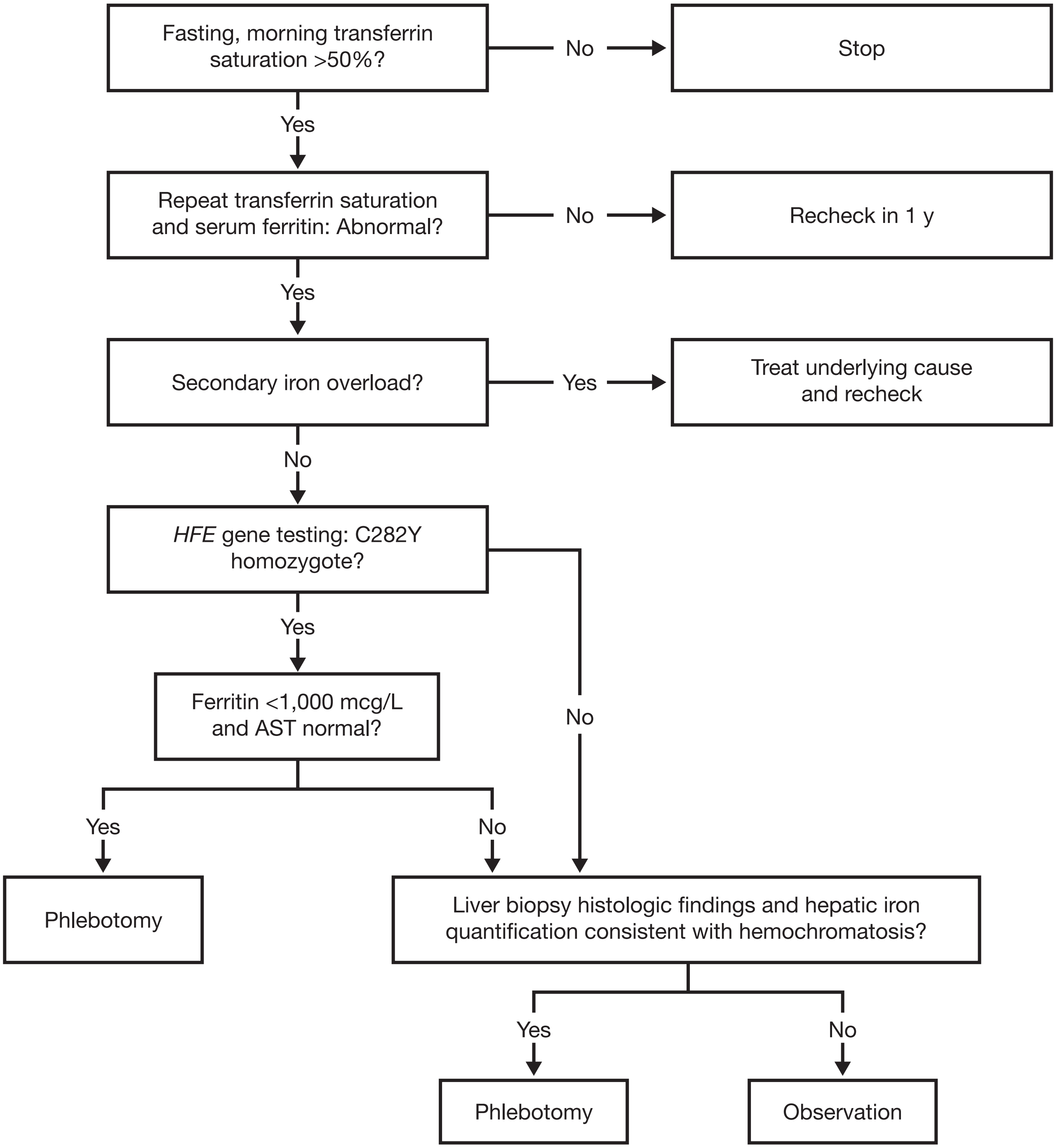
Fasting, morning transferrin saturation >50%?
No
Stop
Yes
Repeat transferrin saturation and serum ferritin: Abnormal?
No
Recheck in 1 y
Yes
Secondary iron overload?
Yes
Treat underlying cause and recheck
No
HFE gene testing: C282Y homozygote?
Yes
No
Ferritin <1,000 mcg/L and AST normal?
Yes
No
Phlebotomy
Liver biopsy histologic findings and hepatic iron quantification consistent with hemochromatosis?
Yes
No
Phlebotomy
Observation

Figure 22.7. *Diagnostic Algorithm for Genetic Hemochromatosis. Causes of secondary iron overload include anemias with ineffective erythropoiesis, multiple blood transfusions, and oral or parenteral iron supplementation. AST indicates aspartate aminotransferase.*

(Modified from Brandhagen DJ, Fairbanks VF, Batts KP, Thibodeau SN. Update on hereditary hemochromatosis and the HFE gene. Mayo Clin Proc. 1999 Sep;74[9]:917-21; used with permission of Mayo Foundation for Medical Education and Research.)

Patients with hemochromatosis should be treated with phlebotomy if the ferritin level is high. Those with C282Y homozygosity and a normal ferritin value can be observed every 2 to 3 years without treatment. The standard for phlebotomy is to remove 500 mL weekly to achieve a ferritin concentration less than 50 μg/L or iron saturation less than 50%. A maintenance program of phlebotomy 4 to 8 times annually is then required. When initiated in the precirrhotic stage, removal of iron can render the liver normal and may improve cardiac function and control of diabetes mellitus. Treatment does not reverse arthropathy or hypogonadism, nor does it eliminate the increased risk of HCC (30%) if cirrhosis has already developed. All first-degree relatives of patients should be evaluated for hemochromatosis.

Wilson Disease

Wilson disease is an autosomal recessive disorder characterized by increased amounts of copper in tissues. The basic defect involves an inability of the liver to prepare copper for biliary excretion. The liver is chiefly involved in children and adolescents, whereas neuropsychiatric manifestations are more prominent in older patients. The Kayser-Fleischer ring is a brownish pigmented ring at the periphery of the cornea. It is not invariably present and is seen more commonly in patients with neurologic manifestations. Hepatic manifestations of Wilson disease are varied and include acute liver failure (often accompanied by hemolysis and renal failure), chronic hepatitis, steatohepatitis, and insidiously developing cirrhosis. The development of HCC is rare. Neurologic signs include tremor, rigidity, altered speech, and changes in personality. Fanconi syndrome and premature arthritis may occur.

Evidence of hemolysis (levels of total bilirubin increased out of proportion to direct bilirubin), a low or normal ALP value, and a low serum uric acid value (due to uricosuria) suggest Wilson disease. The diagnosis is established on the basis of a low ceruloplasmin level and an increased urinary or hepatic concentration of copper. Ceruloplasmin levels may be misleading—they may be increased by inflammation or biliary obstruction and decreased by liver failure of any cause. High concentrations of copper in the liver are found in Wilson disease, although similarly high values can also occur in cholestatic syndromes. Genetic testing for Wilson disease is available but is currently most reliable for screening among first-degree relatives when a specific mutation in the proband has been identified. Standard treatments for Wilson disease are penicillamine, which chelates and increases the urinary excretion of copper, and trientine. Zinc inhibits absorption of copper by the gastrointestinal tract and can be used as adjunctive therapy. All siblings of patients should be evaluated for Wilson disease. Liver transplant corrects the metabolic defect of the disease.

α_1-Antitrypsin Deficiency

The enzyme α_1-antitrypsin is synthesized in the liver. The gene is on chromosome 14. M is the common normal allele, and Z and S are abnormal alleles harboring mutations that cause abnormal folding. Patients with the ZZ phenotype are at highest risk for liver disease. Inability to excrete abnormally folded mutant α_1-antitrypsin results in its intrahepatic accumulation. Patients with α_1-antitrypsin deficiency may have a history of jaundice during the first 6 months of life. In later childhood or adulthood, cirrhosis may develop. Patients with α_1-antitrypsin–induced liver disease often lack clinically important lung disease, and infusions of α_1-antitrypsin do not protect against hepatic involvement. The prevalence of cirrhosis in patients with the MZ phenotype is likely increased, but the risk is small. HCC may complicate α_1-antitrypsin deficiency when cirrhosis is present, especially in males. α_1-Antitrypsin deficiency is diagnosed by determining the α_1-antitrypsin phenotype or genotype. The serum levels of α_1-antitrypsin may vary and can be unreliable. Liver transplant corrects the metabolic defect and changes the recipient's phenotype to that of the donor.

Acute Liver Failure

Acute liver failure is hepatic failure that includes encephalopathy developing less than 8 weeks after the onset of jaundice in patients with no history of liver disease. The common causes are listed in Box 22.1. Acute liver failure due to acetaminophen hepatotoxicity or hepatitis A carries a better prognosis than acute liver failure due to other causes. Markers of poor prognosis include a drug-induced cause (other than acetaminophen), older age, grade 3 or 4 encephalopathy, acidosis, and INR greater than 3.5. Treatment is supportive, and patients

Box 22.1 • Common Causes of Acute Liver Failure

- Infective
  - Hepatitis virus A, B, C (rare), D, and E
  - Herpesvirus
- Drug reactions and toxins
  - Acetaminophen hepatotoxicity
  - Idiosyncratic drug reaction
- Herbal supplements
- Vascular
  - Ischemic hepatitis (shock liver)
  - Acute Budd-Chiari syndrome
- Metabolic
  - Wilson disease
  - Fatty liver of pregnancy
- Miscellaneous
  - Massive malignant infiltration
  - Autoimmune hepatitis

should be transferred to a medical center where liver transplant is available.

Drug-Induced Liver Injury

Drugs cause toxic effects in the liver in different ways, often mimicking liver disease from other causes. With the notable exception of acetaminophen hepatotoxicity, most drug-induced liver disorders are idiosyncratic and not dose-related. Drug-induced liver injury accounts for 2% of the cases of jaundice in hospitalized patients and 50% of the cases of acute liver failure. Consequently, all drugs that have been used by a patient with liver disease must be identified.

Acetaminophen toxicity is the most common cause of acute liver failure. Toxicity may occur at relatively low doses (eg, 3 g daily) in persons with alcoholism because alcohol induces hepatic microsomal cytochrome P450 enzymes, which metabolize acetaminophen to its toxic metabolite. Acetaminophen hepatotoxicity is characterized by aminotransferase values greater than 5,000 U/L and often by renal failure. *N*-acetylcysteine should be given to any patient with acute liver failure in whom acetaminophen toxicity is suspected.

Valproic acid, tetracycline, and zidovudine may cause severe microvesicular steatosis associated with encephalopathy. Hepatotoxicity due to amiodarone may have histologic features that mimic those of alcoholic hepatitis or NAFLD. Antituberculous agents that may cause acute hepatitis include isoniazid, rifampin, and ethambutol. Antibiotics are frequently associated with acute hepatitis. Amoxicillin-clavulanate is a relatively common cause of drug-induced liver injury and may result in prolonged cholestasis that can mimic obstruction of the large bile duct. Nitrofurantoin and minocycline toxicity can mimic autoimmune hepatitis. The chance of hepatotoxicity from lipid-lowering agents is extremely remote, even in patients with preexisting liver disease. Multiple herbal supplements have been implicated in cases of drug-induced liver injury and acute liver failure; thus, it is necessary to elicit a careful history regarding supplement use in such patients.

Liver Tumors

Hepatocellular Carcinoma

In the United States, 90% of HCC cases occur in patients with cirrhosis. The α-fetoprotein level is increased in only 50% of patients with HCC; however, an α-fetoprotein level greater than 400 ng/mL in a patient with cirrhosis and a liver mass is essentially diagnostic of HCC. In patients with cirrhosis, a lesion that enhances in the hepatic arterial phase and shows "washout" in the portal venous phase on contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) is especially suggestive of HCC, and biopsy is often not necessary for diagnosis. Common metastatic sites are lymph nodes, lung, bone, and brain. Liver transplant is an option for patients with limited disease burden (≤3 lesions each <3 cm or a single lesion <5 cm). Transplant is advised particularly for patients with cirrhosis who may not tolerate resection because of poor liver reserve. Transarterial chemoembolization, radioembolization, and percutaneous ablative techniques, such as alcohol injection or radiofrequency ablation, may be useful as primary or neoadjuvant therapy.

Cholangiocarcinoma

The incidence of cholangiocarcinoma is increasing in the United States. Recognized risk factors are PSC, chronic biliary infection, and a history of choledochal cysts. Cholangiocarcinoma may be difficult to diagnose, especially in patients with PSC. For most patients, surgical resection is the treatment of choice, although resection is not possible in many patients. At some centers, liver transplant is considered in select patients with cholangiocarcinoma.

Hepatic Adenoma

Hepatic adenomas are associated with the use of oral contraceptives or estrogen. Hepatic adenomas most commonly present as incidentally discovered liver mass lesions, although they also can present with acute right upper quadrant pain and hemodynamic compromise because of bleeding. Avoidance of estrogens is advised for patients with hepatic adenomas.

Cavernous Hemangioma

Cavernous hemangioma is the most common benign tumor of the liver. CT or MRI with intravenous contrast is often diagnostic, demonstrating peripheral enhancement of the lesion. Cavernous hemangiomas generally require no treatment and are not estrogen dependent.

Focal Nodular Hyperplasia

Focal nodular hyperplasia (FNH) is a benign liver lesion that is probably a reaction to aberrant arterial flow to the liver. These lesions are typically discovered incidentally, although large lesions that stretch the liver capsule may cause abdominal pain. Diagnosis can usually be made with imaging; the characteristic findings are intense vascular enhancement on the hepatic arterial phase and a central scar. Bleeding from FNH is rare and malignant transformation does not occur; therefore, resection is not necessary. Similar to cavernous hemangioma, FNH is not estrogen dependent.

Metastases

Metastases are more common than primary tumors of the liver. Frequent primary sites are the colon, stomach, breast, lung, and pancreas. Surgical resection of isolated colon cancer metastases has a limited effect on long-term survival.

KEY FACTS

- ✓ Genetic hemochromatosis—
  - autosomal recessive: *HFE* gene mutation C282Y is present in 80%-90% of affected patients
  - transferrin saturation >50%: earliest biochemical abnormality
  - high ferritin levels indicate tissue iron overload
  - treatment: phlebotomy to prevent cirrhosis and other end-organ complications
- ✓ Wilson disease—
  - rare autosomal recessive disorder
  - characterized by ineffective biliary excretion of copper
  - presentation: liver disease (more common in children and adolescents) or neuropsychiatric symptoms
  - Kayser-Fleischer ring: brown pigmented ring at periphery of cornea
  - diagnosis: low serum ceruloplasmin levels and high copper levels in urine or liver
  - consider Wilson disease if patient has acute liver failure and hemolysis
- ✓ α_1-Antitrypsin deficiency—
  - patients with ZZ phenotype are at greatest risk for liver disease
  - α_1-antitrypsin infusions do not protect against liver damage (unlike in lung disease)
- ✓ Acetaminophen toxicity—typically, AST >5,000 U/L and ALT >5,000 U/L
- ✓ HCC—
  - in the United States, usually occurs with cirrhosis
  - serum α-fetoprotein level is often increased (>400 ng/mL strongly suggests HCC)

Complications of End-Stage Liver Disease

Most complications of cirrhosis are due to the development of portal hypertension. The mechanism of portal hypertension is related to increases in both portal vein blood flow and intrahepatic resistance to flow. Increased flow is related to splanchnic vasodilatation. Increased resistance is related to sinusoidal narrowing from fibrous tissue and regenerative nodules as well as to active vasoconstriction from alterations in production of endothelin and nitric oxide.

Ascites

The pathogenesis of ascites involves stimulation of the renin-angiotensin-aldosterone system, which results in inappropriate renal sodium retention with expansion of plasma volume. Pleural effusion (*hepatic hydrothorax*) occurs in 6% of patients with cirrhosis and is right-sided in 67%. Edema usually follows ascites and is related to hypoalbuminemia and possibly to increased pressure on the inferior vena cava by the intra-abdominal fluid. The sudden onset of ascites should raise the possibility of hepatic venous outflow obstruction (Budd-Chiari syndrome).

Paracentesis is indicated at initial patient evaluation to confirm the cause of ascites. Tests most useful for determining the cause of ascites are measurements of total protein and the serum-ascites albumin gradient (SAAG), which is calculated as

$$\text{SAAG} = [\text{Serum Albumin}] - [\text{Ascitic Fluid Albumin}].$$

A SAAG of 1.1 g/dL or more indicates portal hypertension. Ascites due to portal hypertension induced by congestive heart failure can be distinguished from cirrhotic ascites because congestive heart failure (and other conditions associated with hepatic venous outflow obstruction such as Budd-Chiari syndrome) usually has an ascitic fluid protein value of 2.5 g/dL or more. Ascites from peritoneal carcinomatosis or tuberculosis generally has an ascitic fluid protein value of 2.5 g/dL or more and a SAAG of less than 1.1 g/dL (Table 22.7).

The treatment of ascites involves dietary sodium restriction and diuretics. Spironolactone (100-200 mg daily) and furosemide (20-40 mg daily) are typically used initially. The goal is to increase the concentration of urinary sodium and to allow the loss of 1 L of ascitic fluid (1 kg of body weight) per day. Paracentesis should be performed therapeutically in patients with tense ascites or with respiratory compromise from abdominal distention. Large-volume or even total paracentesis in combination with administering 6 to 8 g of albumin for each liter of ascitic fluid removed is safe and well tolerated. Refractory ascites is uncommon. Patients with cirrhotic ascites have a low concentration of urinary sodium (<10 mEq/mL on a random specimen) despite maximal diuretic therapy. Those who do not adhere to dietary sodium restriction excrete more than 80 mEq in 24 hours. For patients with refractory or resistant ascites, most physicians advocate therapeutic paracentesis as needed. A transjugular intrahepatic portosystemic shunt (TIPS) is effective in some patients with refractory ascites and is particularly useful for patients with cirrhosis with pleural effusion as the main manifestation of fluid retention. Peritoneovenous shunts are complicated by disseminated intravascular coagulation and shunt malfunction and are rarely used. Patients with cirrhotic ascites, particularly those with refractory ascites, should be considered for a liver transplant.

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) occurs in 10% to 20% of patients with cirrhosis who have ascites. SBP is a bacterial

Table 22.7 • Use of the Serum-Ascites Albumin Gradient (SAAG) and Ascites Protein to Determine the Cause of Ascites

	Ascites Protein	
SAAG, g/dL	**<2.5 g/dL**	**≥2.5 g/dL**
≥1.1	Portal hypertension due to cirrhosis	Portal hypertension due to hepatic venous outflow obstruction (including right-sided heart failure)
<1.1	Nephrotic syndrome	Cancer, tuberculosis

infection of ascitic fluid, typically with enteric gram-negative rods, without an intra-abdominal source of infection. Fever, abdominal pain, and abdominal tenderness are classic symptoms; however, many patients have few or no symptoms. SBP should be considered in any patient with cirrhotic ascites, particularly if there has been clinical deterioration. For all patients with ascites, diagnostic paracentesis is advisable as an initial step. Unless coagulopathy and thrombocytopenia are severe (INR >2.5 or platelet count <10×10^9/L), they are not contraindications for diagnostic paracentesis. A blood cell count and culture of ascitic fluid should be performed for all patients in whom SBP is being considered. Bedside inoculation of blood culture bottles with ascitic fluid increases the diagnostic yield of fluid cultures. SBP is more common in patients with large-volume ascites and in patients with a low ascitic fluid protein concentration (<1.0 g/dL). Also, blood from all patients with SBP should be cultured because almost 50% of these cultures are positive. Variants of SBP are listed in Table 22.8.

SBP and culture-negative neutrocytic ascites should be treated, usually with a third-generation cephalosporin. Albumin should also be given (1.5 g/kg on day 1 and 1 g/kg on day 3). Polymicrobial infection of ascitic fluid should prompt a search for an intra-abdominal focus of infection; SBP nearly always involves only 1 organism. Patients with a prior episode of SBP are at high risk for recurrence, and daily prophylactic therapy (usually with oral ciprofloxacin) is recommended. Patients who have had SBP should be considered for a liver transplant.

Table 22.8 • Variants of Spontaneous Bacterial Peritonitis

	Ascitic Fluid		
Condition	**PMN Cell Count, cells/mL**	**Culture Results**	**Management**
Spontaneous bacterial peritonitis	≥250	Positive	Antibiotics
Culture-negative neutrocytic ascites	≥250	Negative	Antibiotics
Bacterascites	<250	Positive	Treat if symptoms of infection are present; otherwise, repeat paracentesis for blood cell count and cultures

Abbreviation: PMN, polymorphonuclear.

Hepatorenal Syndrome

Hepatorenal syndrome is renal failure in the absence of underlying renal pathologic abnormalities in patients with portal hypertension. The differential diagnosis is given in Table 22.9. In patients with cirrhosis and renal insufficiency, hepatorenal syndrome is difficult to distinguish from prerenal azotemia; thus, a brief trial of volume expansion with albumin is indicated. Treatment is supportive, although vasoconstrictors such as midodrine or norepinephrine are used in patients with low blood pressure. After liver transplant, renal function usually improves, although this is confounded by the renal toxicity of the antirejection drugs tacrolimus and cyclosporine.

Key Definition

Hepatorenal syndrome: *renal failure and portal hypertension without renal pathologic abnormalities.*

Hepatic Encephalopathy

Hepatic encephalopathy is a reversible decrease in the level of consciousness of patients with severe liver disease. Disturbed consciousness, personality change, intellectual deterioration, and slowed speech are common manifestations. Patients often have asterixis (flapping tremor). The sudden development of hepatic encephalopathy in patients with stable cirrhosis should prompt a search for bleeding, infection (especially SBP), or electrolyte disturbances; however, simple precipitating events are increased dietary protein concentration, constipation, or sedatives. Serum and arterial ammonia levels are usually increased but are not necessary for diagnosis. Lactulose decreases the nitrogenous compounds presented to the liver and is the first-line treatment of hepatic encephalopathy. Oral nonabsorbable antibiotics such as rifaximin or neomycin are given to patients who do not respond to or tolerate lactulose. Dietary protein restriction is generally not advised because it can contribute to muscle wasting. Patients with hepatic encephalopathy should be considered for a liver transplant.

Variceal Hemorrhage

Esophageal varices are collateral vessels that develop because of portal hypertension. Varices also can occur in other parts of the gut. Most varices in patients with cirrhosis do not hemorrhage, but the mortality rate among patients with a first hemorrhage is 10% to 20%. For patients who have cirrhosis but have not had bleeding, endoscopy to assess for the presence of varices is advised. Patients with moderate-sized or large varices (>5 mm diameter), especially if there are red marks on the varices, should be treated with a nonselective β-blocker (nadolol or propranolol)

Table 22.9 • Differential Diagnosis for Hepatorenal Syndrome

Variable	Prerenal Azotemia	Hepatorenal Syndrome	Acute Renal Failure
Urinary sodium concentration, mmol/L	<10	<10	>30
Urine to plasma creatinine ratio	>30	>30	<20
Urine osmolality	At least 100 mOsm > plasma osmolality	At least 100 mOsm > plasma osmolality	Equal to plasma osmolality
Urine sediment	Normal	Unremarkable	Casts, debris

Modified from Arroyo V, Gines P, Guevara M, Rodes J. Renal dysfunction in cirrhosis: pathophysiology, clinical features and therapy. In: Boyer TD, Wright TL, Manns MP, Zakim D, editors. Zakim and Boyer's hepatology: a textbook of liver disease. 5th ed. Vol 1. Philadelphia (PA): Saunders/Elsevier; c2006. p. 423-52; used with permission.

to prevent bleeding. Endoscopic variceal ligation is an alternative to nonselective β-blockers. An algorithm for the use of endoscopy to assess for esophageal varices is shown in Figure 22.8.

Bleeding from esophageal varices is generally massive. For patients with acute bleeding, early endoscopy is indicated for diagnosis and treatment. Endoscopic therapy consists of band ligation or, less commonly, sclerotherapy. Octreotide decreases portal venous pressure and may also be given for acute variceal bleeding. All patients with cirrhosis who are hospitalized for gastrointestinal tract bleeding should receive prophylactic antibiotics.

Among patients with bleeding from esophageal varices, 80% to 100% have recurrent bleeding within 2 years after the first episode; therefore, secondary prophylaxis is advised. Oral propranolol or nadolol may be used alone to prevent rebleeding in patients with preserved liver function, although the most common recommendation is serial endoscopic variceal ligation in combination with β-blockers until the varices have been obliterated. TIPS is effective in controlling refractory variceal bleeding. The incidence of hepatic encephalopathy after TIPS is 10% to 40%, but this complication usually can be controlled with medical therapy. Patients with bleeding from gastric varices are more likely to require TIPS than those with bleeding from esophageal varices.

Patients with cirrhosis may also have gastrointestinal tract bleeding from portal hypertensive gastropathy. Bleeding from this lesion is usually gradual, and patients frequently have iron deficiency anemia. Treatment is administration of nonselective β-blockers and iron. Any patient with bleeding from varices or portal hypertensive gastropathy should be considered for liver transplant.

Biliary Tract Disease

Gallstones and Cholecystitis

Gallstones can cause uncomplicated biliary pain, acute cholecystitis, common bile duct obstruction with cholangitis, and acute pancreatitis. Biliary pain is generally felt in the epigastrium or right upper quadrant and is usually severe and steady, lasting several hours. History is important; constant pain, food intolerance, and gaseousness are generally not features of biliary disease. Gallstones do not cause abnormal liver test results unless the common bile duct is obstructed or the patient has sepsis. Ultrasonography is 90% to 97% sensitive for detecting gallbladder stones. Cholecystitis may be suggested by gallbladder contraction, marked distention, surrounding fluid, or wall thickening. Ultrasonography also offers the opportunity to detect dilated bile ducts. If performed during an episode of

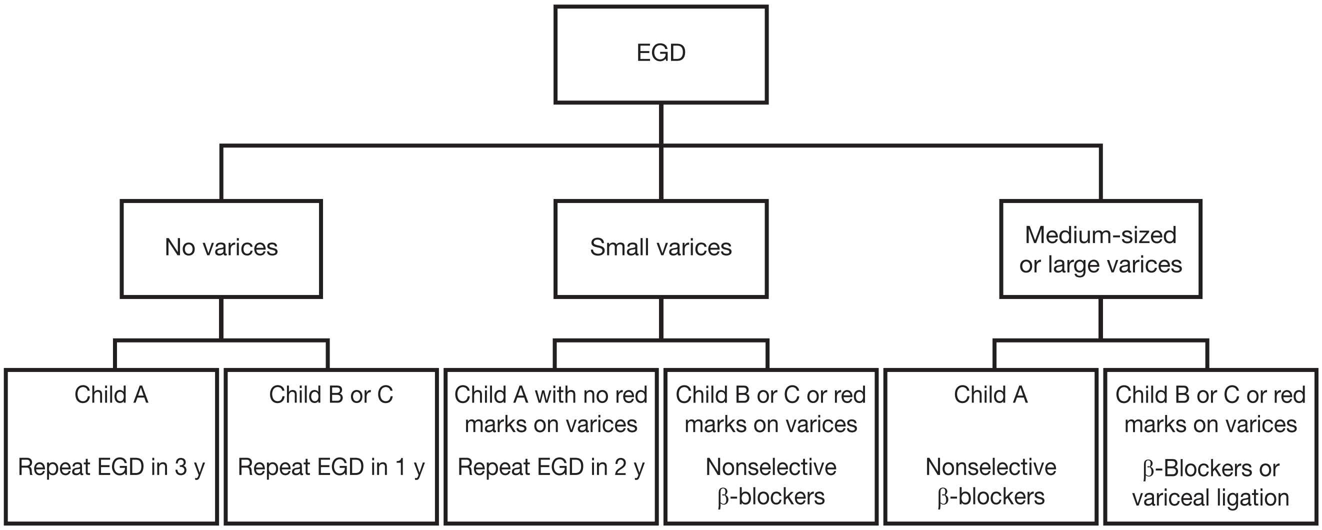
EGD
No varices
Small varices
Medium-sized or large varices
Child A
Repeat EGD in 3 y
Child B or C
Repeat EGD in 1 y
Child A with no red marks on varices
Repeat EGD in 2 y
Child B or C or red marks on varices
Nonselective β-blockers
Child A
Nonselective β-blockers
Child B or C or red marks on varices
β-Blockers or variceal ligation

Figure 22.8. Prophylaxis of Esophageal Variceal Bleeding in Patients With Cirrhosis. Child indicates Child-Pugh class (A, B, or C, in order of increasing severity of cirrhosis); EGD, esophagogastroduodenoscopy.

pain, radionuclide biliary scanning is helpful in diagnosing cystic duct obstruction with cholecystitis. Positive test results are marked by nonvisualization of the gallbladder despite biliary excretion of radioisotope into the small intestine.

Gallstones require no therapy in asymptomatic patients, even in high-risk patients. Acalculous cholecystitis, probably precipitated by prolonged fasting and gallbladder ischemia, generally occurs only in patients hospitalized with critical illnesses. Clinical manifestations are fever and abdominal pain; liver test results may not be abnormal. Diagnosis is made with ultrasonography or radionuclide biliary scan. Patients with episodes of biliary colic or acute cholecystitis should have cholecystectomy. Patients with high surgical risk may undergo drainage with percutaneous cholecystostomy or an endoscopically placed cystic duct stent.

Many patients without gallstones have undergone cholecystectomy because a decrease in gallbladder ejection fraction was noted on radionuclide biliary scan. In most of these patients, pain does not resolve; therefore, a decreased gallbladder ejection fraction should be interpreted with caution because the patient's symptoms often are unrelated to the finding.

Bile Duct Stones

Most bile duct stones originate in the gallbladder, although a few patients, such as those with preexisting biliary disease (eg, PSC), have primary duct stones. CT and ultrasonography are relatively insensitive for common bile duct stones, and diagnosis generally requires MRCP, ERCP, or endoscopic ultrasonography. ERCP also offers therapeutic potential for patients with bile duct stones and is the test of choice if clinical suspicion is high. Patients with bile duct stones can have minimal or no symptoms, or they can have life-threatening cholangitis with abdominal pain, fever, and jaundice. Common bile duct stones should be removed; in nearly all patients, this can be accomplished with ERCP. The urgency of the procedure depends on the clinical presentation. Patients with minimal symptoms can have elective ERCP, but those with cholangitis and fever unresponsive to antibiotics should have urgent endoscopic treatment. Patients with gallbladder stones who have a sphincterotomy and clearance of their duct stones have only a 10% chance of having additional problems with their gallbladder stones; thus, cholecystectomy can be avoided in patients who are at high risk for complications with surgery.

Ascending Cholangitis

Ascending cholangitis occurs when infection develops within an obstructed biliary system, typically due to obstruction from a common bile duct stone. The classic presentation is with Charcot triad: right upper quadrant pain, fever, and jaundice. Patients may have sepsis at initial evaluation. Blood cultures should be obtained to help guide antimicrobial therapy, but infection is typically with enteric gram-negative bacilli. Patients should receive prompt antibiotic therapy and biliary decompression (typically by ERCP with stone extraction or biliary stenting).

Malignant Biliary Obstruction

Malignant biliary obstruction is usually the result of carcinoma of the head of the pancreas, bile duct cancer, or metastases to hilar nodes. As opposed to acute obstruction from biliary stone disease (which is typically painful), malignant biliary obstruction typically presents with painless jaundice and often unintentional weight loss. If the disease is unresectable, palliative endoscopic stenting is as effective as surgical bypass. Patients with malignant biliary obstruction and impending duodenal obstruction are usually considered for palliative surgery, although endoscopic techniques such as duodenal stenting can be attempted by expert endoscopists.

Gallbladder Carcinoma

Gallbladder carcinoma has a strong association with a calcified gallbladder wall (ie, *porcelain gallbladder*); therefore, prophylactic cholecystectomy is advised. In most patients, gallbladder carcinoma is at an advanced stage at presentation and carries a poor prognosis.

KEY FACTS

✓ SAAG—
  - most useful for diagnosing cause of ascites
  - SAAG >1.1 g/dL indicates portal hypertension

✓ Ascites treatment—dietary sodium restriction and diuretic therapy; paracentesis for tense ascites

✓ SBP—
  - may occur with few or no symptoms
  - polymorphonuclear cell count ≥250 cells/mL is diagnostic

✓ Esophageal varices—patients with massive bleeding require resuscitation, endoscopic band ligation, octreotide infusion, and prophylactic antibiotics

✓ Gallstones do not cause abnormal liver test results unless common bile duct is obstructed or patient has sepsis

✓ Acalculous cholecystitis—
  - usually only in patients hospitalized with critical illnesses
  - manage with percutaneous cholecystostomy tube if patient has high surgical risk

✓ Bile duct stones—
  - patients may have life-threatening cholangitis with abdominal pain, fever, and jaundice
  - can usually be removed with ERCP

✓ Malignant biliary obstruction—
  - usually results from carcinoma of the head of the pancreas
  - treatment: palliative endoscopic stenting

23

Pancreatic Disorders

SHOUNAK MAJUMDER, MD

Classification of Pancreatitis

***Acute pancreatitis* is** a reversible inflammation. The 2 types are interstitial pancreatitis and necrotizing pancreatitis. **Interstitial pancreatitis**, in which perfusion of the pancreas is intact, accounts for 80% to 85% of cases and has a mortality rate less than 1%. **Necrotizing pancreatitis** is more severe and results when perfusion is compromised, causing necrosis of pancreatic parenchyma, the peripancreatic tissue, or both. It accounts for 15% to 20% of cases; the mortality rate is 10% if tissue is not infected and 30% if infected.

Key Definitions

Interstitial pancreatitis: *acute pancreatitis in which perfusion of the pancreas is intact.*

Necrotizing pancreatitis: *acute pancreatitis in which perfusion of the pancreas is compromised.*

Chronic pancreatitis is irreversible (ie, structural disease is present, often accompanied by endocrine or exocrine insufficiency). It is documented by pancreatic calcifications on abdominal radiography, parenchymal and ductal abnormalities on endoscopic ultrasonography (EUS), ductal abnormalities on endoscopic retrograde cholangiopancreatography (ERCP), fibroinflammatory changes on pancreatic biopsy, endocrine insufficiency (diabetes mellitus), or exocrine insufficiency (fat malabsorption).

Acute Pancreatitis

In acute pancreatitis, activation of pancreatic enzymes causes autodigestion of the gland. The clinical features are abdominal pain, nausea and vomiting (“too sick to eat”), ileus, peritoneal signs, hypotension, and an abdominal mass.

Causative Factors

Approximately 80% of acute pancreatitis episodes are due to either gallstones or alcohol ingestion. A substantial increase (>3 times the upper limit of the reference range) in aspartate aminotransferase or alanine aminotransferase value in a patient with acute pancreatitis generally indicates that gallstones are the cause. The third most common cause is idiopathic (≈10% of cases).

Medications cause less than 5% of cases of pancreatitis. The following drugs have been reported to cause pancreatitis: azathioprine, 6-mercaptopurine, L-asparaginase, hydrochlorothiazide diuretics, sulfonamides, sulfasalazine, tetracycline, furosemide, estrogens, valproic acid, pentamidine (both parenteral and aerosolized), and the antiretroviral drug didanosine. Evidence that the following drugs cause pancreatitis is less convincing: corticosteroids, nonsteroidal anti-inflammatory drugs, methyldopa, procainamide, chlorthalidone, ethacrynic acid, phenformin, nitrofurantoin, enalapril, erythromycin, metronidazole, non–sulfa-linked aminosalicylate derivatives such as 5-aminosalicylic acid, incretin-based drugs, and interleukin 2.

Other causes include hypertriglyceridemia, which may cause pancreatitis if the triglyceride level is greater than 1,000 mg/dL. Specifically, hyperlipoproteinemia types I, IV, and V with associated oral contraceptive use may be causative. Hypertriglyceridemia

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may mask hyperamylasemia. Hypercalcemia may also cause pancreatitis, especially in the setting of underlying multiple myeloma, hyperparathyroidism, or metastatic carcinoma. In immunocompetent patients, mumps and coxsackievirus cause acute pancreatitis. In patients with acquired immunodeficiency syndrome, acute pancreatitis has been reported with cytomegalovirus infection. Pancreas divisum, or incomplete fusion of the dorsal and ventral pancreatic ducts, may predispose some people to acute pancreatitis, although this is controversial.

Gene mutations and polymorphisms are associated with acute (and chronic) pancreatitis, including mutations in the genes encoding serine protease 1 (*PRSS1*), serine peptidase inhibitor, Kazal type 1 (*SPINK1*), and cystic fibrosis transmembrane conductance regulator (*CFTR*).

Clinical Presentation

Pain may be mild to severe; it is usually sudden in onset and persistent. Typically, the pain is located in the upper abdomen and radiates to the back. Relief may be obtained by bending forward or sitting up. The ingestion of food or alcohol commonly exacerbates the pain.

Fever, if present, is low grade, rarely exceeding 38.3°C in the absence of complications. A fever higher than 38.3°C suggests infection.

Most patients are *hypovolemic* because of vasodilation associated with systemic inflammation; in severe cases, fluid can accumulate in the abdomen.

Patients with pancreatitis may have a mild increase in the total bilirubin level, but they usually *do not* have clinical jaundice. When jaundice is present, it generally results from obstruction of the common bile duct by stones, compression by an inflammatory or necrotic peripancreatic fluid collection, or inflamed pancreatic tissue.

A wide range of *pulmonary manifestations* may occur. More than half of all patients with acute pancreatitis have some degree of hypoxemia, usually from pulmonary shunting. Patients often have atelectasis and may have pleural effusions.

Diagnosis

A diagnosis of acute pancreatitis requires the presence of at least 2 of the following 3 diagnostic criteria:

1. Abdominal pain consistent with acute pancreatitis
2. Serum lipase or amylase levels that are at least 3 times the upper limit of the reference range
3. Findings consistent with acute pancreatitis on cross-sectional imaging.

The diagnosis of acute pancreatitis is challenging during early stages in the absence of advanced morphologic changes of gland destruction and functional impairment.

Serum Amylase and Lipase

Determination of the serum level of amylase is the most useful test for diagnosing acute pancreatitis. The level of amylase increases 2 or 3 hours after the onset of acute pancreatitis and remains increased for 3 or 4 days. The magnitude of the increase does not correlate with the clinical severity. Serum amylase levels may be normal in some patients (<10%) because of alcohol consumption or hypertriglyceridemia. A persistent increase suggests a complication such as pseudocyst, abscess, or ascites. Serum amylase is cleared by the kidney, so the urinary amylase level remains increased after the serum amylase level returns to normal. Isoenzyme identification may aid in distinguishing between salivary (ie, nonpancreatic) and pancreatic sources.

Serum lipase levels may help distinguish between pancreatic hyperamylasemia and an ectopic source of amylase (lung, ovarian, or esophageal carcinoma). The duration of increased levels is longer for lipase than for amylase after acute pancreatitis.

If the amylase level is mildly increased and the patient has a history of vomiting but no signs of obstruction, esophagogastroduodenoscopy could be performed to rule out a penetrating ulcer.

Nonpancreatic Hyperamylasemia

Nonpancreatic hyperamylasemia may result from parotitis; renal failure; macroamylasemia; intestinal obstruction, infarction, or perforation; ruptured ectopic pregnancy; diabetic ketoacidosis; drugs (eg, morphine); burns; pregnancy; and neoplasm (lung, ovary, or esophagus).

Physical Findings

Physical findings in patients with acute pancreatitis include tachycardia, orthostasis, fat necrosis, and xanthelasmas of the skin. The Grey Turner sign (flank discoloration) and the Cullen sign (periumbilical discoloration) suggest retroperitoneal hemorrhage. The abdominal findings often are less impressive than the degree of the patient's pain.

Imaging Studies

A chest radiograph showing an isolated left pleural effusion strongly suggests pancreatitis; infiltrates may indicate aspiration pneumonia or acute respiratory distress syndrome. Abdominal plain radiographs often show the sentinel loop sign (a dilated loop of bowel over the pancreatic area) and the colon cutoff sign (abrupt cutoff of gas in the transverse colon); in contrast, pancreatic calcifications indicate chronic pancreatitis.

Ultrasonographic examination is the procedure of choice for helping to determine whether gallstones are the cause of acute pancreatitis. Although ultrasonography gives limited information about the pancreas, it is the best method for delineating gallstones.

Computed tomography (CT) is indicated for ruling out necrotizing pancreatitis in critically ill patients and for evaluating patients with atypical symptoms or minimally increased serum pancreatic enzyme levels. CT is not required for patients with documented mild interstitial acute pancreatitis.

Treatment

Supportive care is the basis of treatment, along with monitoring for complications and treating them if they occur.

Fluids

Intravascular fluid volume should be restored and maintained; usually this can be accomplished with crystalloids and peripheral intravenous catheters. Fluid therapy must be carefully tailored to avoid volume overload. Blood pressure, pulse, urine output, daily intake and output, and weight should be monitored. Medications that may cause pancreatitis should be discontinued. The use of a nasogastric tube does not shorten the course or severity of pancreatitis, but it should be used for ileus or severe nausea and vomiting.

Analgesics

Common practice has been to use meperidine (75-125 mg intramuscularly every 3-4 hours) instead of morphine because meperidine purportedly causes less spasm of the sphincter of Oddi. Meperidine, however, has potentially toxic metabolites, so it has been removed from many hospital formularies, and the in vivo link between meperidine and sphincter spasm is unclear. Standard methods of analgesia can generally be used without restriction. The efficacy of antisecretory drugs (eg, H_2-receptor antagonists, anticholinergic agents, somatostatin, and glucagon) has not been documented.

Nutrition

Patients with mild acute pancreatitis who do not have organ failure or necrosis can be started on a low-fat oral diet at the time of admission. Patients with severe pancreatitis may require supplemental nutrition, which should be considered if oral feeding cannot be tolerated within 3 to 5 days of hospitalization. This should be provided by means of a nasoenteric tube. Total parenteral nutrition is unnecessary in most cases of pancreatitis and should be considered only if enteral feeding has failed or is not feasible.

Antibiotics

There is no role for prophylactic antibiotics in pancreatitis, regardless of severity. Antibiotics are indicated in patients with necrotizing pancreatitis if infection is suspected (because of an otherwise unexplained fever and gas bubbles in areas of pancreatic necrosis on CT).

Sphincterotomy

Endoscopic sphincterotomy is indicated if acute pancreatitis is associated with cholangitis. ERCP has no role in the diagnosis of acute pancreatitis and should be avoided because it may cause infection and may worsen the pancreatitis.

Complications

Local complications of acute pancreatitis include acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection, and walled-off necrosis. Local complications should be suspected if the patient has persistent or recurrent pain and organ dysfunction. Acute pancreatitis can also cause splenic and portal vein thrombosis. Peripancreatic fluid associated with interstitial pancreatitis with no necrosis can mature over time (>4 weeks) to form an encapsulated collection of fluid with a well-defined inflammatory wall termed a **pseudocyst.** In 50% to 80% of patients, this resolves in 6 to 12 weeks without intervention. Acute necrotic collections mature after 4 weeks to form walled-off necrosis. A pancreatic abscess develops, typically 2 to 4 weeks after the acute episode, and causes fever (>38.3°C), persistent abdominal pain, and persistent hyperamylasemia. If a pancreatic abscess is not drained surgically, the mortality rate is nearly 100%. Antibiotics that are effective for gram-negative and anaerobic organisms should be used. Jaundice results from obstruction of the common bile duct. Pancreatic ascites results from disruption of the pancreatic duct or a leaking pseudocyst.

Key Definition

Pseudocyst: *an encapsulated collection of fluid with a well-defined inflammatory wall.*

A well-recognized systemic complication of acute pancreatitis is acute respiratory distress syndrome. Circulating lecithinase probably splits fatty acids off lecithin, which produces a faulty surfactant. Pleural effusion occurs in approximately 20% of patients with acute pancreatitis. Aspirate analysis shows a high amylase content. Fat necrosis may be due to increased levels of serum lipase.

Assessment of Severity

Most patients with acute pancreatitis recover without any sequelae. The overall mortality rate among patients with acute pancreatitis is 5% to 10%, and death is most often due to hypovolemia and shock, respiratory failure, pancreatic abscess, or systemic sepsis. Laboratory study results, including increased hematocrit and serum urea nitrogen levels, may be helpful in predicting which patients have severe pancreatitis. The Modified Marshall scoring system has replaced the Ranson criteria for the classification of acute pancreatitis (Table 23.1).

Table 23.1 • Modified Marshall Scoring System

		Score[a]				
Organ System	**Measure**	**0**	**1**	**2**	**3**	**4**
Respiratory	PaO_2/FIO_2	>400	301-400	201-300	101-200	≤101
Renal	Serum creatinine, mcmol/L[b]	≤134	134-169	170-310	311-439	>439
Cardiovascular	Systolic BP, mm Hg[c]	>90	<90 Fluid responsive	<90 Not fluid responsive	<90, pH <7.3	<90, pH <7.2

Abbreviations: BP, blood pressure; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen, arterial.

[a] A score ≥2 in any system defines the presence of organ failure.

[b] The score for patients with preexisting chronic renal failure depends on the extent of further deterioration of baseline renal function. No formal correction exists for a baseline serum creatinine ≥134 mcmol/L or ≥1.4 mg/dL.

[c] Off inotropic support.

From Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis: 2012: revision of the Atlanta classification and definitions by international concensus. Gut. 2013 Jan;62(1):102-11; used with permission.

KEY FACTS

✓ Acute pancreatitis—
  - reversible inflammation
  - interstitial pancreatitis (perfusion is intact): 80% of cases (<1% mortality rate)
  - necrotizing pancreatitis (perfusion is compromised): 20% of cases but more severe (10% mortality rate if noninfected; 30% mortality rate if infected)

✓ Chronic pancreatitis—irreversible (presence of structural disease with endocrine or exocrine insufficiency)

✓ Causes of acute pancreatitis—
  - gallstones or alcohol cause 80% of episodes
  - if gallstones, expect increased aspartate aminotransferase or alanine aminotransferase level (>3 times upper limit of reference range)

✓ Diagnosis of acute pancreatitis—measurement of serum amylase level is the most useful test

✓ Physical findings in acute pancreatitis—retroperitoneal hemorrhage is suggested by the Grey Turner sign (flank discoloration) and the Cullen sign (periumbilical discoloration)

✓ Analgesia in acute pancreatitis—use standard methods

✓ Assessment of severity of acute pancreatitis—results of laboratory studies, including increased hematocrit and serum urea nitrogen level, may be helpful

Chronic Pancreatitis

Long-term alcohol use (≥10 years of heavy consumption) is the most common cause of chronic pancreatitis. Gallstones and hyperlipidemia usually do not cause chronic pancreatitis. Patients with recurrent acute pancreatitis can have disease progression to chronic pancreatitis.

Hereditary pancreatitis is caused by a mutation in the serine protease 1 gene (*PRSS1*), which is inherited as an autosomal dominant trait with variable penetrance. Onset is usually before age 20 years, although in 20% of patients it presents after age 20 years. Hereditary pancreatitis is marked by recurring abdominal pain, positive family history, and pancreatic calcifications. It may increase the risk of pancreatic cancer.

Triad of Chronic Pancreatitis

Chronic pancreatitis presents with abdominal pain. In addition, the triad of chronic pancreatitis consists of pancreatic calcifications, steatorrhea, and diabetes mellitus. Diffuse calcification of the pancreas is due to hereditary pancreatitis, alcoholic pancreatitis, or malnutrition. Focal calcification is due to trauma, islet cell tumor, cystic pancreatic neoplasms, or hypercalcemia. By the time steatorrhea occurs, 90% of the pancreas has been destroyed and lipase output has decreased by 90%.

Diagnosis

Serum amylase and lipase levels may be normal, and stool fat concentration may be normal. If malabsorption is present, the stool fat concentration is greater than 7 g (usually much higher) in 24 hours during a 48- to 72-hour stool collection while the patient is consuming a diet with 100 g of fat.

CT shows calcifications, an irregular pancreatic contour, a dilated duct system, or pseudocysts. ERCP shows protein plugs, segmental duct dilatation, and alternating stenosis and dilatation, with obliteration of branches of the main duct. EUS may show changes of chronic pancreatitis, including hyperechoic stranding, hyperechoic foci, and thickening of the pancreatic duct.

Pain

The mechanism for pain is not clearly defined; it may be due to ductular obstruction. One-third to one-half of patients have a decrease in pain after 5 years. Constant pain is usually not pancreatic in origin and indicates a possible neuropathic origin of pain. The possibility of coexistent disease, such as peptic ulcer, or constipation should be considered. Complications of chronic pancreatitis (eg, biliary stricture, pancreatic ductal stricture, cancer, and vascular thrombosis) should be excluded.

Abstinence from alcohol may relieve the pain. Analgesics such as aspirin or acetaminophen are occasionally used. Celiac plexus blocks relieve pain for 3 to 6 months, but long-term efficacy is less effective. Surgical treatment should be considered only if conservative measures have failed. Patients with a dilated pancreatic duct may have a favorable response to a longitudinal pancreaticojejunostomy (ie, the Puestow procedure).

Malabsorption

Patients have malabsorption of fat, essential fatty acids, and fat-soluble vitamins. The goal of enzyme replacement is to maintain body weight. Diarrhea will not resolve. Enteric-coated or microsphere enzymes are designed to be released at an alkaline pH, thus avoiding degradation by stomach acid. The advantage is that they contain larger amounts of lipase. The disadvantages are that they are expensive, and bioavailability is not always predictable.

Autoimmune Pancreatitis

Autoimmune pancreatitis (AIP) is a form of chronic pancreatitis that is extremely corticosteroid responsive. Among the 2 subtypes of AIP—type 1 and type 2—type 1 AIP usually presents with obstructive jaundice, with either a mass in the head of the pancreas or bile duct strictures mimicking pancreatic cancer. On imaging, the pancreas has a characteristic sausage-shaped appearance, and calcification and ductal dilatation are usually absent. Treatment is with corticosteroids—initially a high dose followed by a rapid taper. Relapses are common, and patients with frequent relapses can be treated with steroid-sparing maintenance therapy with immunomodulators or rituximab. Type 2 AIP often affects younger persons and commonly presents as acute pancreatitis. Type 2 AIP is associated with inflammatory bowel disease. Management is similar to initial therapy for type 1 AIP; relapses are relatively uncommon, so maintenance therapy is rarely necessary.

Pancreatic Ductal Adenocarcinoma

Pancreatic ductal adenocarcinoma is more common in men than women and usually presents between age 60 and 80 years. It is currently the third leading cause of cancer-related death in the United States. The 5-year survival rate for all stages combined is less than 10%. Risk factors include diabetes mellitus, chronic pancreatitis, hereditary pancreatitis, carcinogens, benzidine, cigarette smoking, family history of pancreatic cancer in first-degree relatives, and obesity. At initial evaluation, patients with pancreatic ductal adenocarcinoma are usually late in the course of the disease. They may have a vague prodrome of malaise, anorexia, and weight loss. Symptoms may be overlooked until pain or jaundice develops. Two signs associated with pancreatic cancer are the **Courvoisier sign** (painless jaundice with a palpable gallbladder) and the **Trousseau sign** (recurrent migratory thrombophlebitis). New-onset diabetes mellitus and nonbacterial thrombotic endocarditis may be associated with pancreatic cancer.

Key Definitions

Courvoisier sign: *painless jaundice with a palpable gallbladder.*

Trousseau sign: *recurrent migratory thrombophlebitis.*

Routine laboratory blood analysis has limited usefulness. Patients may have increased levels of liver enzymes, amylase, and lipase or anemia, although this is variable. The only currently available tumor marker, CA 19-9, is nonspecific. Abdominal ultrasonography and CT are each approximately 80% sensitive in localizing pancreatic masses. The "double duct" sign on CT is a classic feature with obstruction of the pancreatic duct and the bile duct. Either imaging method may be used in conjunction with fine-needle aspiration biopsy or surgical biopsy to make a tissue diagnosis. If a mass in the pancreas is found on CT and deemed resectable, surgical consultation should be pursued as the next step (additional testing may not be necessary). ERCP and EUS are used if the abdominal ultrasonographic or CT results are inconclusive. ERCP and EUS each have sensitivity greater than 90%. With combined EUS-ERCP, brushings and biopsies can be performed in an attempt to confirm the diagnosis.

Surgery is the only treatment that offers hope for cure; however, most lesions are not resectable. Surgery has no role in patients with metastatic disease. Most patients with resectable lesions are treated with chemotherapy with or without radiation before surgery to optimize the chances of a tumor-free resection margin.

Cystic Fibrosis

Because patients with cystic fibrosis are living longer, internists should know the common intestinal complications of this disease. Exocrine pancreatic insufficiency (malabsorption) is the most important complication and is quite common (85%-90%

of patients). Endocrine pancreatic insufficiency (diabetes mellitus) occurs in 20% to 30% of patients. Rectal prolapse occurs in 20% of patients, and a distal small-bowel obstruction from thick secretions occurs in 15% to 20%. Focal biliary cirrhosis develops in 20% of patients.

Pancreatic Endocrine Tumors

Zollinger-Ellison syndrome is a non–beta islet cell tumor of the pancreas that produces gastrin and causes gastric acid hypersecretion. This results in peptic ulcer disease (see Peptic Ulcer Disease subsection in Chapter 21, "Esophageal and Gastric Disorders").

Key Definition

Zollinger-Ellison syndrome: *a non–beta islet cell tumor of the pancreas that produces gastrin, causes hypersecretion of gastric acid, and results in peptic ulcer disease.*

Insulinoma is the most common islet cell tumor. It is a beta islet cell tumor that produces insulin and causes hypoglycemia. The diagnosis is based on finding increased fasting plasma levels of insulin and hypoglycemia. CT, EUS, or arteriography may be useful in localizing the tumor.

Glucagonoma is an alpha islet cell tumor that produces glucagon. The typical presentation is with diabetes mellitus, weight loss, and a classic rash (necrolytic migratory erythema). The diagnosis is based on finding increased glucagon levels and that the blood glucose level does not increase after an injection of glucagon.

Pancreatic cholera is a pancreatic tumor that produces vasoactive intestinal polypeptide (VIP), which causes watery diarrhea (see Secretory Diarrhea subsection in Chapter 20, "Diarrhea, Malabsorption, and Small-Bowel Disorders").

Somatostatinoma is a delta islet cell tumor that produces somatostatin, which inhibits insulin, gastrin, and pancreatic enzyme secretion. The result is diabetes mellitus and diarrhea. The diagnosis is based on finding increased plasma levels of somatostatin.

Octreotide is useful in treating pancreatic endocrine tumors except for somatostatinomas. Octreotide prevents the release of hormone and antagonizes hormonal effects on target organs.

KEY FACTS

- ✓ Most common cause of chronic pancreatitis—long-term alcohol use (≥10 years of heavy consumption)
- ✓ Presentation of chronic pancreatitis—
  - abdominal pain
  - triad of chronic pancreatitis: pancreatic calcifications, steatorrhea, and diabetes mellitus
- ✓ Pancreatic ductal adenocarcinoma—
  - 5-year survival rate <10%
  - "double duct" sign on CT (from obstruction of the pancreatic ducts and bile ducts)
- ✓ Insulinoma—the most common islet cell tumor
- ✓ Pancreatic cholera—pancreatic tumor that produces VIP, which causes watery diarrhea

IV

Questions and Answers

Questions

Multiple Choice (Choose the best answer)

IV.1. A 36-year-old woman with ulcerative colitis, well controlled on mesalamine 2.4 g daily, reports a 5-month history of back and buttock pain and stiffness that improves with activity but is beginning to interfere with daily activities, including her job as a trial attorney. She has taken nonsteroidal anti-inflammatory drugs over the counter for 2 weeks and had inadequate relief. Colonoscopy shows quiescent panulcerative colitis. Lumbosacral magnetic resonance imaging shows sacroiliitis. What is the most appropriate therapy?

a. Increase the dose of mesalamine to 4.8 g per day.
b. Discontinue mesalamine and begin sulfasalazine.
c. Continue mesalamine and add methotrexate.
d. Discontinue mesalamine and begin adalimumab.

IV.2. A 38-year-old man is generally healthy but reports that his mother had a diagnosis of stage III colon cancer at age 58 years and died of the disease 2 years later. Her tumor showed intact expression of mismatch repair enzymes by immunohistochemistry. He is the oldest of 3 siblings; the other 2 are not interested in screening and are therefore not known to have any polyps. His father is alive and well at age 70 years. His maternal grandparents died of lung cancer and myocardial infarction, respectively. What is the next step in management?

a. Colonoscopy now
b. Screening colonoscopy at age 40 years
c. Computed tomography (CT) colonography at age 40 years
d. Microsatellite instability testing of the mother's primary tumor tissue

IV.3. A 47-year-old woman is seen for abdominal pain and diarrhea that has been present for much of the past year. She also has been frustrated by her inability to lose weight. Pain is in the left lower quadrant and typically improves only after she passes several loose, nonbloody stools. She reports no constitutional symptoms. She has a history of autoimmune thyroiditis, and is now taking replacement thyroxine. Family history is negative for colorectal cancer. Abdominal examination reveals tenderness to deep palpation in the left and right lower quadrants of the abdomen; guarding and rebound are absent and pain is not exacerbated by straight-leg extension or flexion. Rectal examination demonstrates normal resting tone, squeeze, and descent. What is the best next step in management?

a. Colonoscopy
b. Rifaximin 550 mg twice daily
c. Serum tissue transglutaminase measurement
d. Low-dose tricyclic antidepressant therapy

IV.4. A 26-year-old woman seeks care for a 6-month history of nonbloody diarrhea with 10 lb (4.5 kg) of weight loss. In addition, she reports a pruritic rash on her elbows and knees. She has no relevant family history, no travel, no alcohol use, and no other associated symptoms. Physical examination indicates a well-appearing woman. The abdomen is nontender without hepatosplenomegaly. A peripheral blood smear shows Howell-Jolly bodies and anemia. What is the best next step in management?

a. Computed tomography enterography
b. Glucose-hydrogen breath test
c. Stool culture
d. Serum immunoglobulin (Ig) A tissue transglutaminase measurement

IV.5. A 58-year-old white man is evaluated for chronic abdominal pain and weight loss. He has had migratory arthritis for 5 years with no specific diagnosis, despite consultation with a rheumatologist. He has lost 20 lb (9 kg) in the past 2 years and has had watery diarrhea. His abdominal pain and diarrhea improve with fasting. He reports intermittent fever and night sweats. On physical examination, he is thin and appears chronically ill. He is afebrile with normal vital signs. There is skin hyperpigmentation on the neck and bilateral upper arms, with palpable axillary and inguinal lymph nodes. The abdomen is nondistended with mild tenderness throughout. There is no hepatosplenomegaly. Laboratory evaluation shows mild normocytic anemia and a low serum albumin value of 2.8 g/dL. What is the best next diagnostic test?

a. Upper endoscopy with small bowel biopsies
b. Colonoscopy with random biopsies
c. Abdominal computed tomography
d. *Giardia* stool antigen test

IV.6. A 20-year-old woman is brought to the emergency department with an abrupt onset of lower abdominal cramping pain 5 days after eating out with her boyfriend. She ate a hamburger that was "raw." The boyfriend had chitterlings and is asymptomatic. Mild lower abdominal pain developed initially, which was followed by passage of watery, then bloody, stools. Cramping abdominal pain and bloody diarrhea have persisted. On examination, she is afebrile and nontoxic appearing. Abdominal examination indicates mild, right lower quadrant tenderness without rebound or guarding. Abdominal computed tomography demonstrates segmental thickening of the right-sided colon from cecum to hepatic flexure. Which of the following pathogens is the most likely cause of these symptoms?

a. *Bacillus cereus*
b. *Escherichia coli*
c. *Yersinia enterocolitica*
d. *Clostridium perfringens*

IV.7. A 50-year-old man from Latin America seeks care for a 2-month history of intermittent epigastric pain that has partially responded to proton pump inhibitor (PPI) therapy. He reports no symptoms of gastroesophageal reflux. He takes acetaminophen for chronic low-back pain and does not use nonsteroidal anti-inflammatory drugs. Laboratory tests show a hemoglobin value of 10.4 g/dL and no evidence of leukocytosis. You suspect that his symptoms may be secondary to *Helicobacter pylori* infection. What is the best initial diagnostic test for this patient?

a. Stool antigen assay
b. Urea breath testing
c. Upper endoscopy with gastric biopsies
d. Serologic testing

IV.8. A 55-year-old woman returns to the clinic for further evaluation of postprandial fullness and epigastric burning. One year earlier, *H pylori* had been diagnosed on a stool antigen test. She was treated with a combination of clarithromycin, amoxicillin, and omeprazole for 10 days without resolution of her symptoms. She subsequently underwent upper endoscopy, which showed no evidence of peptic ulcer disease but indicated mild gastritis. Gastric biopsies were negative for *H pylori* organisms. She was started on a trial of 40 mg of omeprazole daily without added benefit. What is the best next step in the treatment of this patient?

a. Increase omeprazole to 40 mg twice daily.
b. Repeat stool antigen test for *H pylori*.
c. Start a low-dose tricyclic antidepressant.
d. Start quadruple therapy for *H pylori* (proton pump inhibitor [PPI], metronidazole, bismuth, and tetracycline).

IV.9. A 55-year-old white man is seen for his yearly physical examination. He quit smoking 2 years ago and reports no alcohol use. His body mass index is 30 kg/m^2. He is participating in a daily exercise program and is trying to lose weight. The patient's only concern is nocturnal regurgitation triggered by overeating. His symptoms have been intermittently present for more than 5 years and improve with over-the-counter antacids. He does not sleep with the head of the bed elevated. He does not report symptoms of dysphagia. What is the best next step in the treatment of this patient?

a. Proton pump inhibitor (PPI)
b. H_2-receptor antagonist before bedtime
c. Gastroesophageal reflux disease (GERD)-related lifestyle modifications
d. Upper endoscopy

IV.10. A 45-year-old woman comes to the emergency department with a 2-week history of jaundice. She has lost 5 kg during this time but was previously well. She drinks 2 or 3 glasses of wine each day. She has taken 2 500-mg acetaminophen tablets each day in the past 2 weeks. On examination, she has icteric sclera and tender hepatomegaly. She is alert and oriented without asterixis. Laboratory studies indicate macrocytic anemia (hemoglobin 10.5 g/dL, mean corpuscular volume 108 fL), leukocytosis (leukocytes 14.9×10^9/L with left shift), and increased liver test values (aspartate aminotransferase [AST] 125 U/L, alanine aminotransferase [ALT] 59 U/L, total bilirubin 12.8 mg/dL). Antinuclear antibodies, viral serologic testing, and ceruloplasmin levels are all normal. Ultrasonography indicates sludge in the gallbladder, a coarse liver echotexture, no ascites, and no biliary dilatation. What is the most likely diagnosis?

a. Nonalcoholic fatty liver disease
b. Alcoholic hepatitis
c. Autoimmune hepatitis
d. Acetaminophen hepatotoxicity

IV.11. A 30-year-old man seeks care for a 2-week history of jaundice, fatigue, and nausea. His travel history is notable for multiple international trips; his most recent was a trip to Mexico about 3 months ago. He frequently stays in rural areas when he travels. The patient drinks 2 to 3 alcoholic beverages daily. He endorses a history of high-risk sexual behaviors. Physical examination shows jaundice, and the liver is mildly enlarged. There is no asterixis. Laboratory findings are as follows: alanine aminotransferase [ALT] 2,210 U/L, total bilirubin 5.8 mg/dL, and INR 1.4. He is positive for IgG anti–hepatitis A virus, hepatitis B surface antigen, IgM anti–hepatitis B core antigen, and hepatitis B e antigen. He is negative for IgG anti–hepatitis B e antigen. What is the most likely diagnosis?

a. Acute hepatitis A
b. Acute hepatitis B
c. Acute hepatitis E
d. Chronic hepatitis B

IV.12. A 53-year-old woman with alcoholism is referred for a 3-month history of abdominal distention, leg edema, and dyspnea. Her history is notable for active smoking, chronic obstructive pulmonary disease, and a positive tuberculin skin test, for which she received isoniazid in the remote past. Physical examination is notable for distant heart sounds, marked ascites, and leg edema. Chest radiography shows mild hyperinflation and a small right pleural effusion. Doppler ultrasonography of the liver shows ascites, a coarse liver echotexture, and patent hepatic and portal veins. Laboratory studies are notable for a total bilirubin value of 2.5 mg/dL, serum albumin value of 2.5 g/dL, and an INR of 1.4. On paracentesis, ascites fluid analysis shows a total protein level of 1.9 g/dL and an albumin level of 0.9 g/dL. The ascites cell count is 300 cells/mL with 50% polymorphonuclear cells. Which of the following is the most likely cause of her ascites?

a. Spontaneous bacterial peritonitis
b. Right ventricular congestive heart failure (cor pulmonale)
c. Alcoholic cirrhosis
d. Peritoneal carcinomatosis

IV.13. A 28-year-old woman comes to the emergency department at midnight with acute epigastric pain, nausea, and vomiting. On examination, she has a low-grade fever and is hemodynamically stable. She has mild tenderness in the upper abdomen without peritoneal signs. Her white blood cell count is 16.5×10^9/L, serum bilirubin level is 4.2 mg/dL, and lipase level is 3,432 IU/L. Transabdominal ultrasonography indicates a mildly distended gallbladder without stones or wall thickening. There is a small amount of pericholecystic and peripancreatic fluid. The extrahepatic bile duct measures 10 mm in diameter. She is admitted to the hospital; management is with bowel rest and fluid resuscitation. The next morning she is in persistent pain requiring fentanyl patient-controlled analgesia, and her total bilirubin level is now 4.8 mg/dL. What is the best next step in management?

a. Urgent cholecystectomy
b. Endoscopic retrograde cholangiopancreatography (ERCP)
c. Conservative management
d. Nasoenteric tube and initiation of feeding

IV.14. A 52-year-old man with chronic pancreatitis has chronic abdominal pain requiring daily narcotic analgesics. He has no history of diabetes mellitus and reports no weight loss or steatorrhea. Pancreas-protocol computed tomography shows pancreatic parenchymal calcification and a focal stricture in the main pancreatic duct with upstream duct dilatation measuring 7 mm. What is the best next step in management?

a. Pancreaticojejunostomy
b. Pancreatic enzyme replacement therapy
c. Endoscopic retrograde cholangiopancreatography and pancreatic duct stenting
d. Celiac plexus block

IV.15. A 55-year-old man with no history of alcohol use or smoking seeks care for painless jaundice. Abdominal computed tomography shows a mass in the head of the pancreas with a normal-appearing pancreatic duct. Blood levels of immunoglobulin (Ig) G4 are increased and CA 19-9 levels are normal. Endoscopic ultrasound-guided biopsy shows benign pancreatic acini and inflammatory cells without evidence of a malignant process. What is the most likely diagnosis?

a. Pancreatic ductal adenocarcinoma
b. Solid pseudopapillary neoplasm
c. Klatskin tumor
d. Autoimmune pancreatitis

Answers

IV.1. Answer d.

The objective of this question is to recognize inflammatory arthritis as an extraintestinal manifestation of inflammatory bowel disease and determine the approach to its management. Large-joint pauciarticular arthritis (knee, hip) activity often parallels luminal inflammatory bowel disease activity. Axial inflammatory arthritis, such as sacroiliitis and ankylosing spondylitis, will not parallel bowel disease activity, will not respond well to disease-modifying antirheumatic drugs (DMARDs; eg, sulfasalazine and methotrexate), and will frequently require anti-TNFα therapy (eg, adalimumab). The dose of mesalamine should not be increased because the patient has axial arthritis and her ulcerative colitis is under good control, both symptomatically and at mucosal assessment by colonoscopy. DMARDs may be used for small-joint peripheral arthritis, which may respond well; caution should be used when prescribing methotrexate to women of childbearing age (pregnancy category X).

IV.2. Answer b.

The objective of the question is to recognize patients at increased risk for colorectal cancer on the basis of family history. The US Preventive Services Task Force (USPSTF) 2016 guidelines on colorectal cancer screening defer to other guidelines on risk assessment, based on family history. This patient's first-degree relative was younger than 60 years at diagnosis, which increases the patient's risk. In this situation, the Multi-Society Task Force (MSTF) guideline on colorectal cancer screening recommends colonoscopy every 5 years beginning at age 40 years or at an age 10 years before the affected relative's age at diagnosis; thus, 40 years is the correct age to begin his screening. CT colonography would be a good option for average-risk screening or for follow-up of incomplete colonoscopy but is not an appropriate surveillance test for this high-risk patient. Microsatellite instability testing is an alternative to immunohistochemistry for assessment of mismatch repair enzyme deficiency. Since the patient's pedigree is not consistent with hereditary nonpolyposis colon cancer and the mother's tumor was normal by immunohistochemistry, there is no need to obtain microsatellite instability testing. For patients with a first-degree relative with a colorectal cancer diagnosis at or older than 60 years, the MSTF advises that any of the USPSTF-endorsed average-risk screening tests be applied beginning at age 40 years.

IV.3. Answer c.

The patient has longstanding symptoms of abdominal pain that improves after a change in stool habit. Patients suspected of having diarrhea-predominant irritable bowel syndrome (IBS-D) should undergo serum tissue transglutaminase testing to exclude celiac disease, especially because she has another autoimmune disorder. She does not have alarm features to strongly suggest an underlying organic disease of the colorectum and is too young to begin colorectal cancer screening. The patient will most likely meet criteria for IBS-D, but therapy specifically directed to this disorder, such as rifaximin, should not be started until evaluation is complete. Low-dose tricyclic therapy may be appropriate for functional dyspepsia but is not a first-line therapy for IBS-D.

IV.4. Answer d.

This young woman with chronic diarrhea, weight loss, and iron deficiency anemia most likely has celiac disease. The presence of Howell-Jolly bodies on peripheral blood smear (nuclear remnants within red blood cells) suggests splenic hypofunction, which is seen in approximately 15% of patients with celiac disease. The correct answer is to obtain serum IgA tissue transglutaminase measurement, which is the serologic test of choice to diagnose celiac disease. In addition, a small-bowel biopsy showing a malabsorptive pattern of injury is required. The diagnosis of celiac disease requires 3 criteria to be met: 1) serologic findings positive for celiac disease, 2) compatible small-bowel histologic findings, and 3) response to a gluten-free diet. If any 1 of the diagnostic criteria is not met, the diagnosis of celiac disease is in question. Computed tomography enterography may help diagnose Crohn disease, which can present with diarrhea and iron deficiency anemia; however, the peripheral blood smear findings make Crohn disease unlikely. A glucose-hydrogen breath test can assess for small-intestinal bacterial overgrowth, which can present with diarrhea and weight loss but would not cause iron deficiency and splenic hypofunction. Routine stool culture tests for *Salmonella, Shigella*, and *Campylobacter,* which are not causes of chronic diarrhea, would be of low yield in this case.

IV.5. Answer a.

The most likely diagnosis in this case is Whipple disease, which is a rare multisystem infectious disease caused by *Tropheryma whipplei*. The disease occurs most commonly in middle-aged white men. Diarrhea, abdominal pain, and weight loss are common clinical manifestations. A migratory arthritis is the most common extraintestinal manifestation and affects most patients. The small bowel is usually involved, regardless of gastrointestinal symptoms. Thus, the primary diagnostic approach to a patient with suspected Whipple disease is upper endoscopy with small bowel biopsies. Intestinal biopsy specimens show the characteristic finding of blunted, club-shaped villi and infiltration of the lamina propria with periodic acid-Schiff–positive macrophages and dilated lacteals. Polymerase chain reaction assay for *T whipplei* DNA confirms the diagnosis. Colonoscopy with random biopsies would be helpful in diagnosing microscopic colitis by demonstrating collagenous or lymphocytic colitis. Microscopic colitis is unlikely because it is more common in elderly women and is not typically associated with abdominal pain, weight loss, peripheral lymphadenopathy, and skin hyperpigmentation. Abdominal computed tomography would be useful to further assess for mesenteric adenopathy, which can be seen in Whipple disease but would not be diagnostic. *Giardia* stool antigen testing is the diagnostic test of choice for giardiasis, which is unlikely in this case because it does not cause the extraintestinal manifestations of peripheral adenopathy and migratory arthritis.

IV.6. Answer b.

This young woman has hemorrhagic colitis related to Shiga toxin–producing *Escherichia coli* (STEC) acquired from eating raw ground beef. Shiga toxins are cytotoxins that damage vascular endothelial cells in target organs of the gut and kidney. Clues to the diagnosis of STEC infection are the onset of bloody diarrhea without fever and the 5-day incubation period. STEC infections usually begin with watery diarrhea that becomes bloody. Despite the presence of bloody diarrhea, fever is unusual. The incubation period of STEC ranges from 3 to 8 days, and the infection is typically acquired from ingestion of ground beef, unpasteurized apple cider, and vegetables including alfalfa sprouts. In 10% of patients, hemolytic-uremic syndrome develops, which is diagnosed about 1 week after the beginning of the diarrheal illness, when diarrhea is resolving. It is diagnosed by Shiga toxin–based assays, and antibiotic treatment is contraindicated. *Bacillus cereus* can cause 2 types of food poisoning syndromes: a short-incubation (1 to 6 hours) emetic syndrome and a long-incubation (10 to 16 hours) diarrheal syndrome. The diarrheal syndrome of *B cereus* is toxin mediated and characterized by a short-lived, nonbloody diarrhea; it is often acquired from ingesting fried rice, which makes it unlikely in this case. Although *Yersinia enterocolitica* is a foodborne illness that can cause an inflammatory diarrhea with abdominal pain, fever is typically present and it is associated with consumption of undercooked pork (chitterlings, which her boyfriend ate). *Clostridium perfringens* causes a watery diarrhea after spores of *C perfringens* germinate in foods such as meats, poultry, or gravy. After ingestion of the organism, the toxin is produced in the host gastrointestinal tract, which then causes efflux of water and ions, leading to diarrhea.

IV.7. Answer c.

This patient's epigastric pain and mild anemia are concerning for peptic ulcer disease that warrants further investigation with upper endoscopy. His recent use of PPIs may affect the diagnostic performance of the stool antigen assay and urea breath test. Stopping PPIs for 1 to 2 weeks is contraindicated given the concern for peptic ulcer disease. Serologic testing does not rule out associated complications in a patient with a high pretest probability of *H pylori* infection.

IV.8. Answer c.

This patient continues to have postprandial fullness and epigastric burning after upper endoscopy has ruled out peptic ulcer disease and *H pylori* infection. Mild gastritis is a common and normal finding on endoscopy and does not explain this patient's symptoms. Functional dyspepsia is common after eradication of *H pylori* infection. A neuromodulator such as a low-dose tricyclic antidepressant has been shown to lead to improvement of symptoms in patients with functional dyspepsia. High-dose PPI therapy is unlikely to provide benefit to a patient who has not responded to daily PPI therapy. Retesting for *H pylori* or empirical treatment are not indicated given the absence of *H pylori* infection on gastric biopsies. Furthermore, the diagnostic performance of the stool antigen test is limited by the use of PPIs.

IV.9. Answer d.

This patient is at risk for GERD-related complications, including Barrett esophagus. Guidelines recommend endoscopic screening for Barrett esophagus in obese white men older than 50 years with a history of chronic GERD. GERD lifestyle modifications include weight loss, avoidance of trigger foods and late meals, and sleeping with the head of the bed at an incline. This patient would benefit from GERD lifestyle modifications and may also need acid suppression with a PPI or H_2-receptor antagonist after endoscopic evaluation. Long-term use of PPI therapy may be warranted in patients with GERD-related complications such as erosive esophagitis or Barrett esophagus.

IV.10. Answer b.

This patient has acute hepatitis in the setting of alcohol misuse. The threshold for alcoholic liver injury in women occurs at more than 1 drink per day. In clinical practice, many patients may underestimate the serving size of their alcoholic beverages (each "drink" containing more than 1 serving of alcohol). The clinical features of alcoholic hepatitis include macrocytosis, leukocytosis, a 2:1 AST:ALT ratio, and tender hepatomegaly. Although nonalcoholic fatty liver disease can cause abnormal liver test results, it does not present with acute hepatitis. Autoimmune hepatitis is less likely in the setting of a negative antinuclear antibody. Acetaminophen hepatotoxicity typically causes ALT increases of more than 5,000 U/L, and the dose taken by this patient is not typically enough to cause hepatotoxicity.

IV.11. Answer b.

This patient has an acute hepatitis, and the serologic findings are consistent with acute hepatitis B. His hepatitis A serologic findings are consistent with immunity to hepatitis A. Acute hepatitis A and E are both possible but serologically ruled out. Chronic hepatitis B is ruled out by the acute nature of the hepatitis.

IV.12. Answer c.

The serum-ascites albumin gradient (SAAG) in this case is 1.6 and the total ascites protein level is low. Therefore, the ascites chemistry findings are consistent with portal hypertension from cirrhosis. Spontaneous bacterial peritonitis would have a polymorphonuclear cell count (not total cell count) of more than 250 cells/mL. Congestive heart failure would cause ascites with both a high SAAG and a high protein concentration. Peritoneal carcinomatosis would cause ascites with a low SAAG and a high protein concentration.

IV.13. Answer b.

The triad of acute abdominal pain, increased lipase level, and peripancreatic fluid confirms a diagnosis of acute pancreatitis. Jaundice in a patient with acute pancreatitis suggests a biliary etiology. A markedly dilated bile duct and bilirubin levels >4 mg/dL are strongly suggestive of choledocholithiasis, and prompt biliary decompression with ERCP is indicated in a patient with clinical features of cholangitis (Charcot triad: pain, jaundice, and fever). Endoscopic removal of a bile duct stone, when suspected, should be performed before cholecystectomy. Conservative treatment would be reasonable if pain improves and bilirubin starts decreasing, which indicate spontaneous passage of a bile duct stone. Initiation of nasoenteric feeding within 24 hours after admission is not superior to attempting an oral diet at 72 hours, with nasoenteric feeding started only if oral feeding is not tolerated.

IV.14. Answer a.

Pain control is one of the most difficult challenges in the management of chronic pancreatitis. Current evidence suggests that surgery (ie, pancreaticojejunostomy) is superior to endoscopic therapy and pancreatic duct stenting for pain relief in patients with a dilated pancreatic duct. The patient does not have steatorrhea, so there is no indication for pancreatic enzyme replacement. Because it provides only transient improvement in pain and has a risk of complications, celiac plexus block is generally not recommended for patients with painful chronic pancreatitis in the absence of concomitant pancreatic cancer.

IV.15. Answer d.

Autoimmune pancreatitis is a form of corticosteroid-responsive chronic pancreatitis. Patients most commonly have a pancreatic mass and jaundice that mimic pancreatic cancer. Biopsies are negative for cancer, and treatment with corticosteroids often results in prompt improvement. IgG4 is a serologic marker of this disease. CA 19-9 is a marker of pancreatic ductal adenocarcinoma, and malignant tumors of the head of the pancreas typically result in obstruction and dilatation of the main pancreatic duct. Solid pseudopapillary neoplasm is a low-grade malignant cystic lesion of the pancreas usually affecting young women. Klatskin tumor refers to hilar cholangiocarcinoma, a malignant tumor of the bile ducts.

Section

V

General Internal Medicine

24 Clinical Epidemiology

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Interpretation of Diagnostic Tests

Diagnostic tests are tools that either increase or decrease the likelihood of disease in a specific patient. When a diagnostic test is applied to a population at risk for a particular disease, patients in the studied population can be assigned to 1 of 4 groups on the basis of disease status and the test result. Table 24.1 illustrates the concept.

By convention, the 4 groups are assigned the letters *a* for true positive (TP), *b* for false positive (FP), *c* for false negative (FN), and *d* for true negative (TN) (Table 24.2). On the basis of this table (called a *2×2 table*), several test characteristics can be defined.

Sensitivity

Sensitivity refers to a positive test result for a patient with the disease. The *TP rate* is the proportion of patients with the disease who have a positive test result:

$$\text{Sensitivity} = \frac{\text{TP}}{\text{TP} + \text{FN}}$$

The 2×2 table definition of *sensitivity* is a/(a+c). The following rules are related to sensitivity.

1. If a test has 100% sensitivity, a negative test result rules *out* the disorder (mnemonic: *SN out*).
2. Screening tests are used to maximize sensitivity and avoid missing a person who has the disease.
3. Characteristics of a test are not affected by the prevalence of disease in the population.

Specificity

Specificity refers to a negative test result for a patient without the disease. The *TN rate* is the proportion of patients without the disease who have a negative test result:

$$\text{Specificity} = \frac{\text{TN}}{\text{TN} + \text{FP}}$$

The 2×2 table definition of *specificity* is d/(b+d). The following rules relate to specificity.

1. If a test has 100% specificity, a positive test result rules *in* the disorder (mnemonic: *SP in*).
2. Confirmatory tests are used in follow-up to maximize specificity and avoid incorrectly classifying a healthy person as having disease.
3. Characteristics of a test are not affected by the prevalence of disease in the population.

Positive Predictive Value

When a patient's illness is evaluated through interpretation of a diagnostic test result, the 2×2 table is read horizontally, not vertically. In this case, one wants to know whether a patient with a positive test result actually has the disease—that is, how well does the test result predict a disease compared with the reference standard for that disease? Thus, in the 2×2 table, the horizontal rows for the diagnostic test result are of primary interest. Among all patients with a positive diagnostic test result (TP+FP), in what proportion, $\frac{\text{TP}}{\text{TP} + \text{FP}}$, has the diagnosis been predicted correctly or ruled in? This proportion is the **positive predictive value** (PPV). PPV is the proportion of patients who have the disease among all the patients who test positive for the disease. It provides information most useful in clinical practice. PPV is affected by the prevalence of the disease in the population. The 2×2 table definition of PPV is $\frac{\text{TP}}{\text{TP} + \text{FP}} = \text{a}/(\text{a} + \text{b})$.

Table 24.1 • Four Outcomes of a Diagnostic Test

Outcome	Disease Status	Test Result
True positive	Present	Abnormal
False positive	Absent	Abnormal
False negative	Present	Normal
True negative	Absent	Normal

Negative Predictive Value

It also is important to know the percentage of patients with a negative test result (FN+TN) who actually do not have the disease. This proportion, $\frac{\text{TN}}{\text{FN}+\text{TN}}$, is the **negative predictive value** (NPV). NPV is the proportion of patients who do not have the disease of interest among all the patients who test negative for the disease. NPV is affected by the prevalence of disease in the population. The 2×2 table definition of NPV is

$$\frac{\text{TN}}{\text{FN}+\text{TN}} = \text{d}/(\text{c}+\text{d}).$$

Prevalence

Prevalence is defined as the proportion of persons with the disease in the population to whom the test has been applied. In terms of the 2×2 table, prevalence is written as follows.

$$\frac{\text{TP}+\text{FN}}{\text{TP}+\text{FP}+\text{FN}+\text{TN}} = \frac{\text{a}+\text{c}}{\text{a}+\text{b}+\text{c}+\text{d}}$$

Key Definitions

Sensitivity: *positive (test) in disease.*

Specificity: *negative (test) in health.*

Key Definitions

Positive predictive value: *proportion of patients who have the disease among all patients who test positive for the disease.*

Negative predictive value: *proportion of patients who do not have the disease among all patients who test negative for the disease.*

How to Construct a 2×2 Table

The sensitivity, specificity, and predictive values of normal and abnormal test results can be calculated with even a limited amount of information. For example, a new diagnostic test is positive in 90% of patients who have the disease and is negative in 95% of patients who are disease-free. The prevalence of the disease in the tested population is 10%. This provides the following information: sensitivity equals 90%, specificity equals 95%, and prevalence equals 10%.

Table 24.2 • A 2×2 Table for Diagnostic Tests

		Target Disorder		
		Present	**Absent**	
Diagnostic Test Result	**Positive**	True Positive a	False Positive b	a+b
	Negative	c False negative	d True negative	c+d
		a+c	b+d	a+b+c+d

Prevalence = (a+c)/(a+b+c+d)
Test characteristics
  Sensitivity = a/(a+c)
  Specificity = d/(b+d)
Frequency-dependent properties
  Positive predictive value = a/(a+b)
  Negative predictive value = d/(c+d)

This test is now ready to be applied to a group of patients by filling in a 2×2 table (Table 24.3). The calculation is often easier if the test is applied to a large number of patients. For example, if it is applied to 1,000 patients, a+b+c+d = 1,000.

Because the prevalence of the disease is 10%, 100 patients have the disease $(0.1 \times 1{,}000 = 100, \text{ or } a + c = 100)$. Of the patients, 90%, or 900, are disease free $(0.9 \times 1{,}000 = 900, \text{ or } b + d = 900)$.

Sensitivity of 90% means that 90% of the 100 patients with disease have a positive test result ($a = 0.9 \times 100 = 90$) and 10% have a negative result ($c = 0.1 \times 100 = 10$).

Specificity of 95% means that 95% of the 900 patients who are disease-free have a negative test result ($d = 0.95 \times 900 = 855$) and 5% have a positive test result ($b = 0.05 \times 900 = 45$).

The 2×2 table in Table 24.3 shows that 135 patients (a+b) have a positive test result; however, only 90 of these 135 patients actually have the disease. Therefore, the PPV of a positive test is $\frac{a}{(a+b)} = \frac{90}{135} = 66.7\%$. That is, only two-thirds of all patients with a positive test result actually have the disease. Similarly, one can determine that 865 patients (c+d) have a negative test result; 855 of these 865 patients are disease free. Therefore, the NPV of the test is $\frac{d}{(c+d)} = \frac{855}{865} = 98.8\%$.

Clinicians should be able to perform these simple calculations. Clinical decision making by internists is more likely to

Table 24.3 • A 2×2 Table for a Test With 90% Sensitivity, 95% Specificity, and 10% Prevalence

		Disease Present	**Disease Absent**	
Diagnostic Test Result	**Positive**	90 a	45 b	135 a+b
	Negative	c 10	d 855	c+d 865
		a+c 100	b+d 900	a+b+c+d 1,000

Prevalence = (a+c)/(a+b+c+d) = 100/1,000 = 10%
Test characteristics
Sensitivity = a/(a+c) = 90/100 = 90%
Specificity = d/(b+d) = 855/900 = 95%
Frequency-dependent properties
Positive predictive value = a/(a+b) = 90/135 = 66.7%
Negative predictive value = d/(c+d) = 855/865 = 98.8%
Likelihood ratio (LR) for a positive test result
LR+ = Sensitivity/(1 − Specificity) = 90%/5% = 18
LR for a negative test result
LR− = (1 − Sensitivity)/Specificity = 10%/95% = 0.11
Pretest odds = Prevalence/(1 − Prevalence) = 10%/90% = 0.11
Posttest odds = Pretest odds × LR
Posttest probability = Posttest odds/(Posttest odds + 1)

depend on the PPV and NPV of test results for a given population than on the sensitivity or specificity of the test.

KEY FACTS

- ✓ If a test has 100% sensitivity, a negative test rules *out* the disorder
- ✓ If a test has 100% specificity, a positive test rules *in* the disorder
- ✓ Prevalence—the proportion of persons with the disease in the population to whom the test has been applied
- ✓ Clinical decision making—more likely to depend on PPV and NPV of test results for a given population than on the test's sensitivity or specificity

For example, if the prevalence of the disease in the clinician's population is 2% instead of 10%, the PPV and NPV can be recalculated. The PPV of abnormal test results decreases to 26.9%, which is considerably different from 66.7% (based on a prevalence of 10%), although the test's sensitivity (90%) and specificity (95%) have not changed (Table 24.4).

Table 24.4 • A 2×2 Table for a Test With 90% Sensitivity, 95% Specificity, and 2% Prevalence

		Disease Present	**Disease Absent**	
Diagnostic Test Result	**Positive**	18 a	49 b	67 a+b
	Negative	c 2	d 931	c+d 933
		a+c 20	b+d 980	a+b+c+d 1,000

Prevalence = (a+c)/(a+b+c+d) = 20/1,000 = 2%
Test characteristics
Sensitivity = a/(a+c) = 18/20 = 90%
Specificity = d/(b+d) = 931/980 = 95%
Frequency-dependent properties
Positive predictive value = a/(a+b) = 18/67 = 26.9%
Negative predictive value = d/(c+d) = 931/933 = 99.8%

Use of Odds and Likelihood Ratios

Some physicians prefer to interpret diagnostic test results with the likelihood ratio (LR). This ratio takes properties of a diagnostic test (sensitivity and specificity) and makes them more helpful in clinical decision making. It helps the clinician determine the probability of disease for a specific patient after a diagnostic test has been performed.

The formula for an LR for a positive test result (LR+) is

$$LR+ = \frac{\text{Positive Test in Disease}}{\text{Positive Test in No Disease}} = \frac{\text{Sensitivity}}{1-\text{Specificity}}$$

The formula for an LR for a negative test result (LR–) is

$$LR- = \frac{\text{Negative Test in Disease}}{\text{Negative Test in No Disease}} = \frac{1-\text{Sensitivity}}{\text{Specificity}}$$

For example, if test A has a sensitivity of 95% and a specificity of 90%,

$$LR+ = \frac{\text{Sensitivity}}{1-\text{Specificity}} = \frac{95}{10} = 9.5$$

and

$$LR- = \frac{1-\text{Sensitivity}}{\text{Specificity}} = \frac{5}{90} = 0.06$$

However, if test B has a sensitivity of 20% and a specificity of 80%, then

$$LR+ = \frac{\text{Sensitivity}}{1-\text{Specificity}} = \frac{20}{20} = 1$$

$$LR- = \frac{1-\text{Sensitivity}}{\text{Specificity}} = \frac{80}{80} = 1$$

Table 24.5 • Examples of Symptoms, Signs, and Tests and the Corresponding Likelihood Ratio (LR)

Target Disorder	Patient Population	Health Care Setting	Symptom, Sign, Test	No. of Signs or Symptoms	LR
Alcohol abuse or dependency	Patients admitted to orthopedic or medical services over 6 mo	US teaching hospital	Yes to ≥3 questions on CAGE questionnaire[a]		250
Sinusitis (by further investigation)	Patients with nasal problems	US teaching hospital	Maxillary toothache, purulent nasal secretion, poor response to nasal decongestants, abnormal transillumination findings, or history of colored nasal discharge	≥4	6.4
				3	2.6
				2	1.1
				1	0.5
				0	0.1
Ascites	Male veteran patients	US veterans hospital	Presence of fluid wave (test done by internal medicine residents)		9.6

Abbreviation: CAGE, *c*ut down, *a*nnoyed, *g*uilty, *e*ye-opener.

[a] Screening questionnaire for potential alcoholism.

Data from Bush B, Shaw S, Cleary P, Delbanco TL, Aronson MD. Screening for alcohol abuse using the CAGE questionnaire. Am J Med. 1987 Feb;82(2):231-5; Williams JW Jr, Simel DL. Does this patient have sinusitis? Diagnosing acute sinusitis by history and physical examination. JAMA. 1993 Sep 8;270(10):1242-6; Williams JW Jr, Simel DL, Roberts L, Samsa GP. Clinical evaluation for sinusitis: making the diagnosis by history and physical examination. Ann Intern Med. 1992 Nov 1;117(9):705-10; Williams JW Jr, Simel DL. The rational clinical examination: does this patient have ascites? How to divine fluid in the abdomen. JAMA. 1992 May 20;267(19):2645–8; and Simel DL, Halvorsen RA Jr, Feussner JR. Quantitating bedside diagnosis: clinical evaluation of ascites. J Gen Intern Med. 1988 Sep–Oct;3(5):423-8.

As a general rule, diagnostic tests with an LR+ greater than 10 or an LR– less than 0.1 have a greater influence on the posttest probability of disease (ie, they are better tests) than diagnostic tests with LRs between 10 and 0.1 (and an LR of 1 has no influence at all). In the 2 examples above, test A has reasonable power to rule in or rule out disease and test B is entirely void of any diagnostic utility.

Sample LRs are provided in the following example and in Table 24.5.

Example

A 40-year-old man is admitted to the hospital for pneumonia. He says that he consumes 2 six-packs of beer each week. On the basis of this history and clinical judgment, his physician assumes that he has a pretest probability of 20% for a diagnosis of alcoholism. The physician asks the man questions from the CAGE (*c*ut down, *a*nnoyed, *g*uilty, *e*ye-opener) questionnaire, and his responses are positive for all 4 questions. The LR+ for 3 or more CAGE questions is 250.

At this point, the physician has 2 choices. The first is to use a nomogram (Figure 24.1) and, with a straightedge, connect the pretest probability of 20% and the LR+ of 250 to the posttest probability. This shows that the posttest probability for a diagnosis of alcoholism is 99%.

The second option should be used when there is no nomogram for performing this simple calculation. Without a nomogram, the following steps must be done.

1. Convert the pretest probability to pretest odds.
2. Multiply the pretest odds by the LR to obtain the posttest odds.
3. Convert the posttest odds to posttest probability.

Probability and odds can be converted somewhat interchangeably with the following formulas.

$$\text{Odds} = \frac{\text{Probability}}{1 - \text{Probability}}$$

and

$$\text{Probability} = \frac{\text{Odds}}{1 + \text{Odds}}$$

In the example, step 1 involves converting pretest probability to pretest odds. In this case, the physician estimated that the pretest probability of alcoholism is 20%. With the formulas above, the calculation is the following.

$$\text{Pretest Odds} = \frac{0.20}{1 - 0.20} = 0.25$$

Therefore, 0.25 is the pretest odds of having the condition. Step 2 involves determining the posttest odds for a positive test result. This can be determined by multiplying the pretest odds (0.25) by the LR+ for 3 or more positive questions on the CAGE questionnaire (250): 0.25×250 = 62.5. Step 3 allows conversion of posttest odds to posttest probability by placing the numbers in the following formula.

$$\text{Posttest Probability} = \frac{\text{Odds}}{1 + \text{Odds}} = \frac{62.5}{63.5} = 98.4$$

In conclusion, the posttest probability for the diagnosis of alcoholism for this patient is 98.4%, which is close to the value obtained from the nomogram.

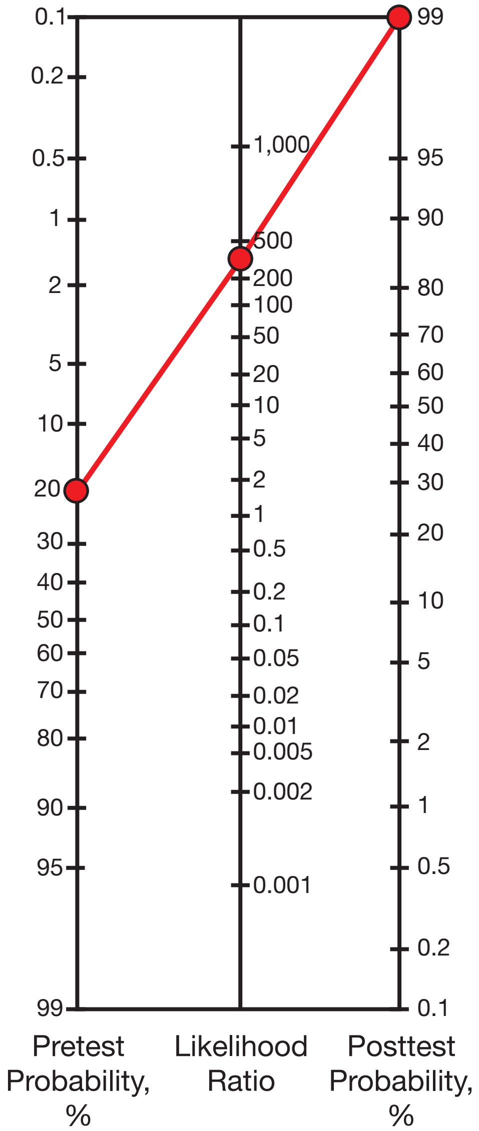


Figure 24.1. *Nomogram.*

Interpretation of Therapeutic Results

Physicians often make treatment decisions on the basis of the results of randomized controlled trials (RCTs). To understand whether the results of such trials are impressive, the physician is required to translate these results into language understandable to both physicians and patients. This terminology also can be used to compare various therapies for the disease of interest. Several authors have coined terms and derived useful equations to help physicians make sense of RCTs concerned with therapy.

Relative Risk Reduction

The results of RCTs of anticoagulant therapy to prevent stroke in patients with atrial fibrillation have been published and summarized. In primary prevention studies, the average 1-year risk of stroke in the placebo group was 5%. Because no therapy was administered to that group, this can be called the *control event rate* (CER). In these studies of patients with atrial fibrillation treated with adjusted-dose warfarin (international normalized ratio [INR], 2.0-3.0), the approximate stroke risk was reduced to 2% per year. This can be called the *experimental event rate* (EER) because the patients received a particular therapy.

The traditional measure often used to report the difference between the treated and untreated groups is the *relative risk reduction* (RRR), which is calculated as $\frac{\text{CER} - \text{EER}}{\text{CER}}$. This measure relates the reduction in risk of the outcome event with the intervention to the baseline risk rate (ie, the CER). In this example, the RRR is $\frac{5\% - 2\%}{5\%} = 60\%$.

Therefore, anticoagulant therapy reduced the yearly risk of a stroke in patients with atrial fibrillation by 60% compared with the baseline risk of a stroke with no therapy. However, the RRR often is not clinically helpful because the number itself does not provide information about the baseline risk rate (ie, the CER). For example, even if only very small percentages of control patients (0.005%) and patients receiving anticoagulation (0.002%) have a stroke, the RRR is unchanged:

$$\frac{0.005\% - 0.002\%}{0.005\%} = 60\%.$$

Therefore, the RRR often is not useful to the clinician or the patient, although a large RRR can be used to make a dramatic endorsement for therapy by proponents of that therapy.

- RRR $\frac{\text{CER} - \text{EER}}{\text{CER}}$
- Often RRR is not clinically useful because it does not provide information about the baseline risk rate.

Absolute Risk Reduction

In the example above, it would be useful for the physician and the patient to know the absolute difference in rates of stroke between the control group and the atrial fibrillation group given anticoagulants (CER–EER). This measure is called the *absolute risk reduction* (ARR). In the combined Stroke Prevention in Atrial Fibrillation (SPAF) trials, the ARR or (CER – EER) = (5% – 2%) = 3% per year.

- ARR = (CER – EER).
- ARR is clinically more useful for interpreting therapeutic results.

Number Needed to Treat

The physician and patient often want to know the number of patients needed to treat (NNT) with a therapy to prevent 1 additional bad outcome. That number can be calculated as

$\frac{1}{\text{ARR}}$. The NNT to prevent 1 stroke by using the adjusted dose of warfarin in patients with atrial fibrillation would be $\frac{1}{0.03} = \frac{1}{3\%} = 33$. Therefore, the NNT would be 33 patients; that is, 33 patients would need to be treated with warfarin (INR, 2.0-3.0) for 1 year to prevent 1 additional stroke.

- NNT identifies the number of patients who need to be treated with a therapy to prevent 1 additional bad outcome.
- $\text{NNT} = \frac{1}{\text{ARR}}$

Number Needed to Harm

Conversely, if the rate of adverse events caused by the experimental therapy is known and compared with the rate of adverse events in the placebo group, the number needed to harm (NNH) can be calculated. This useful number tells the physician how many treated patients it takes to produce 1 additional harmful event. In the SPAF trials, the average risk of intracranial hemorrhage for the group given warfarin was 0.3% per year, compared with 0.1% per year for the placebo group. Therefore, the NNH can be calculated as the reciprocal of the absolute risk increase (ARI). The ARI is calculated by subtracting the harm CER from the harm EER or, in this case, 0.3% – 0.1% = 0.2%. In this example, $\frac{1}{0.2} = \frac{1}{0.002\%} = 500$. Therefore, 500 patients would need to be treated with anticoagulant for 1 year to cause 1 additional intracranial hemorrhage compared with the control group.

- NNH identifies how many treated patients are needed to produce 1 additional harmful event.
- $\text{NNH} = \frac{1}{\text{Harm EER} - \text{Harm CER}}$

KEY FACTS

- ✓ Diagnostic tests with LR+ greater than 10 or LR– less than 0.1 are better tests than those with LRs in between
- ✓ Number needed to treat—how many patients need to be treated with a therapy to prevent 1 additional bad outcome
- ✓ Number needed to harm—how many treated patients are needed to produce 1 additional harmful event

25 Complementary and Alternative Medicine

TONY Y. CHON, MD; BRENT A. BAUER, MD

Complementary and alternative medicine (CAM) has many meanings, each derived in part from its context. Traditionally, CAM has encompassed treatments such as acupuncture, herbs and dietary supplements, massage, and chiropractic. Yet, in recent decades, the explosive growth of research in this arena (largely sponsored by the National Institutes of Health [NIH] National Center for Complementary and Alternative Medicine, now called the National Center for Complementary and Integrative Health) has led to a number of therapies being incorporated increasingly into conventional training and practice. For example, lessons that teach a mind-body practice (eg, meditation) to a patient to help control hypertension are combined with the use of such therapies as medications or lifestyle modifications. This growing integration of evidence-based CAM therapies and conventional medicine is increasingly being referred to as ***integrative medicine***.

Key Definition

Integrative medicine: *the growing integration of evidence-based complementary and alternative medicine therapies and conventional medicine.*

Figure 25.1 reflects survey data from 2002, 2007, and 2012 (N=88,962 adults age ≥18 years). The data suggest that nearly 35% of US adults use some aspect of CAM as part of their health care. However, surveys of specific patient populations (eg, those with cancer, chronic pain, or fibromyalgia) suggest that CAM use may reach 80% to 90% in these groups.

Natural products (ie, herbs and supplements) are the most popular CAM therapy (Figure 25.2). However, the popularity of deep breathing, meditation, massage, yoga, progressive relaxation, and guided imagery also suggests that many patients are turning to CAM to help deal with stress.

Natural products deserve special attention because many can have toxic adverse effects or drug-herb interactions, or both, if not used thoughtfully and carefully.

Herbs and Dietary Supplements

The Dietary Supplement Health and Education Act (DSHEA) of 1994 defines a dietary supplement as "a product (other than tobacco) that is intended to supplement the diet that bears or contains 1 or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or combination" of these ingredients. Table 25.1 outlines common herbs and dietary supplements, their potential uses, and their potential adverse reactions. St John's wort is a commonly used herb and is associated with several potentially serious drug interactions (Table 25.2).

The passage of the DSHEA allowed supplements to be sold with suggested dosages, while at the same time specifically exempting manufacturers from having to demonstrate safety or efficacy of their products. As a result, herbal sales have exploded in the United States in the past 25 years. However, the quality and purity of many products on US shelves were often poor, due in part to relatively limited oversight of the market by the US Food and Drug Administration. The good

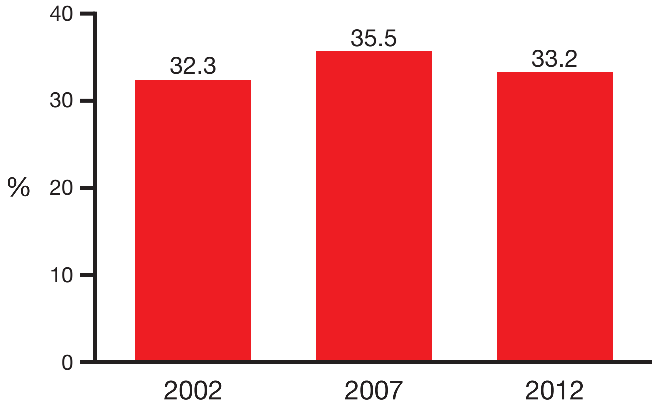


Figure 25.1. *Use of Complementary and Alternative Medicine by US Adults Age 18 Years and Older.*

(Data from Clarke TC, Black LI, Stussman BJ, Barnes PM, Nahin RL. Trends in the use of complementary health approaches among adults: United States, 2002-2012. Natl Health Stat Report. 2015 Feb 10;[79]:1-16.)

manufacturing practice guidelines passed in 2010 now mandate that all supplements manufactured or sold in the United States must contain what the label states and nothing else. Coupled with these developments was a dramatic growth in the quality and quantity of clinical trials on supplements. Physicians can now focus on helping patients make informed decisions about the role of specific supplements in regard to their individual health needs.

KEY FACTS

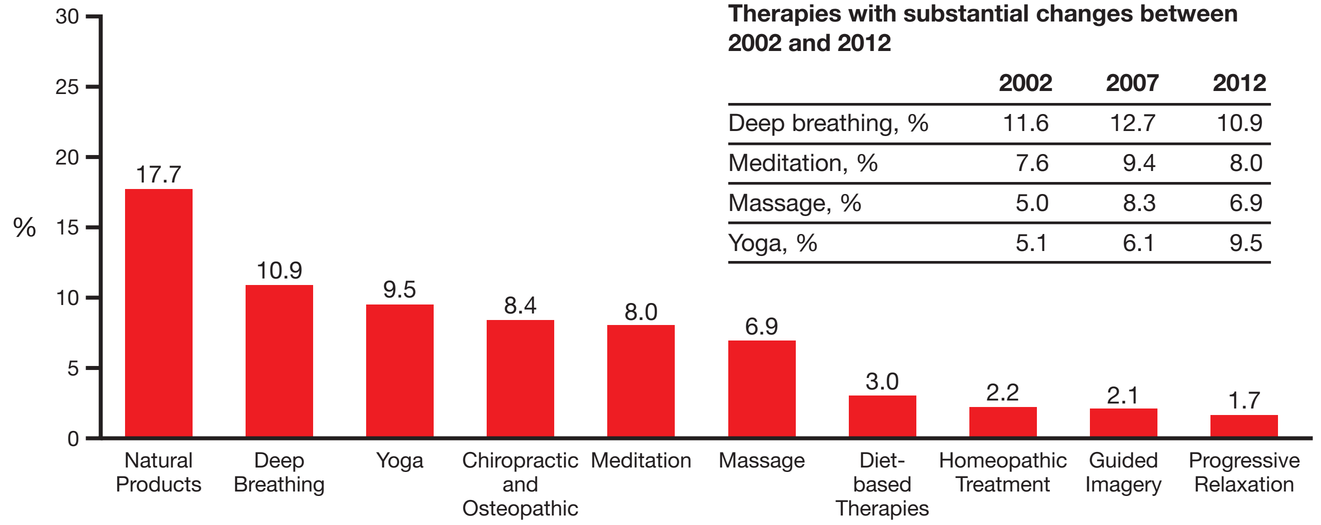
- ✓ CAM therapies—used by nearly 40% of US adults and up to 90% of specific patient populations; natural products are most popular
- ✓ St John's wort can interfere with metabolism of many medications (eg, oral contraceptives, cyclosporine)
- ✓ S-adenosyl-methionine may be useful for osteoarthritis and depression; fish oil, for hypertriglyceridemia
- ✓ Ginkgo—ineffective in more recent large-scale trials
- ✓ Herbs and supplements that may increase risk of bleeding (and may need to be discontinued before a surgical procedure)—garlic, ginger, ginseng, feverfew, fish oil, and vitamin E

Alternative Medical Systems

Alternative medical systems include traditional Chinese medicine, called *ayurveda*, and homeopathy. The major features of each are summarized in Boxes 25.1 through 25.3.

Manual Therapies

Manual therapies include chiropractic and massage therapy. The major features of each are summarized in Boxes 25.4 and 25.5.



Therapies with substantial changes between 2002 and 2012

	2002	2007	2012
Deep breathing, %	11.6	12.7	10.9
Meditation, %	7.6	9.4	8.0
Massage, %	5.0	8.3	6.9
Yoga, %	5.1	6.1	9.5

Figure 25.2. *Ten Most Common Complementary and Alternative Medicine Therapies Among Adults. Natural products indicate dietary supplements other than vitamins and minerals.*

(Modified from Clarke TC, Black LI, Stussman BJ, Barnes PM, Nahin RL. Trends in the use of complementary health approaches among adults: United States, 2002-2012. National health statistics reports; no 79. Hyattsville, MD: National Center for Health Statistics. 2015.)

Table 25.1 • Common Herbs and Dietary Supplements

Herb or Dietary Supplement	Potential Uses	Description	Potential Adverse Reactions	Key Points
Black cohosh	Menopausal symptoms	Also called *black snakeroot* and *bugbane* May have effects similar to estrogen	Gastrointestinal tract discomfort May cause liver damage	Should not be used longer than 6 mo Should not be taken during pregnancy
Echinacea	Cold and flu symptoms	Purported to boost the immune system	May cause allergic reactions	No clear evidence to support efficacy
Garlic	Hypertension, heart disease, hypercholesterolemia	May decrease low-density lipoprotein cholesterol	Breath and body odor, abdominal discomfort May reduce blood clotting ability	May increase risk of bleeding in persons taking anticoagulant medications
Ginger	Nausea from pregnancy, motion sickness, and chemotherapy	Also available as powder, tablet, extract, tincture, and oil	High doses can cause abdominal discomfort May increase risk of bleeding with anticoagulant medications	Not recommended for nausea during pregnancy with history of bleeding disorder or miscarriage
Ginkgo	Memory loss and dementia	Beneficial components believed to be flavonoids and terpenoids	May raise blood pressure with thiazide diuretics May increase risk of bleeding	No clear evidence to support efficacy Should be used cautiously when taking anticoagulant medications
Ginseng	Restore and enhance well-being	Used for allergies, asthma, fatigue, headaches, heart disease, and many other conditions	May raise blood pressure in persons with hypertension	Should not exceed recommended daily doses Should not be used in persons with uncontrolled hypertension
Glucosamine and chondroitin sulfate	Osteoarthritis	Natural compounds found in cartilage	Generally well tolerated No known drug interactions	Research results are mixed
Omega-3 fatty acids (fish oil)	Cardiovascular health, including hypertriglyceridemia	Contain both DHA and EPA Dietary sources include freshwater fish and flaxseed, walnut, canola, and soybean oils	Gastrointestinal discomfort, fishy odor May increase bleeding risk at high doses (>3 g daily)	May reduce triglycerides 20%-50% at dose of 2-4 g daily May lower risk of another heart attack, stroke, or death
S-adenosyl-methionine	Depression, osteoarthritis	Occurs naturally in the human body; not found in food Helps to produce and regulate hormones and cell functioning	Generally well tolerated Gas, nausea, diarrhea, and headaches at higher doses	Holds promise in depression and osteoarthritis; long-term benefits and risks unknown May interact with SSRIs and tricyclic antidepressants
Saw palmetto	Prostatic hyperplasia	Has also been used as sedative and antiseptic	Generally well tolerated	Research results are mixed
Soy	Menopausal symptoms, hypercholesterolemia, osteoporosis, heart disease	Active ingredients include isoflavones and weak forms of estrogen (phytoestrogen)	Generally well tolerated Potential allergy to soy May interact with monoamine oxidase inhibitor antidepressants	Research results are mixed
St John's wort *(Hypericum Perforatum)*	Depression, anxiety, insomnia	Flowers and leaves contain active ingredients (eg, hyperforin)	Generally well tolerated Some active compounds do not mix well with certain prescription drugs[a]	Several studies support its use for treatment of mild to moderate depression Potential serious drug interactions[a]

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; SSRI, selective serotonin reuptake inhibitor.

[a] Potential important interactions with St John's wort are listed in Table 25.2.

Table 25.2 • Potential Important Drug Interactions With St John's Wort

Drug	**Interactions**
Warfarin	Increased breakdown of warfarin that leads to increased risk of clotting
Oral contraceptive pills (OCPs)	Increased breakdown of OCPs that leads to increased risk of pregnancy
Cyclosporine	Increased breakdown of cyclosporine that leads to increased risk of transplant rejection
Digoxin	Increased breakdown of digoxin that leads to decreased medication effectiveness
HIV protease inhibitors	Increased breakdown of protease inhibitors that leads to decreased medication effectiveness
Anticonvulsants (eg, carbamazepine, phenytoin)	Increased breakdown of anticonvulsants that leads to increased risk of seizures
Selective serotonin reuptake inhibitors	Increased serotonin levels that leads to serotonin syndrome

Box 25.1 • Traditional Chinese Medicine

Distinct paradigm of medicine that originated in China thousands of years ago

Paradigm helps to define how to diagnose and treat illness

Focus is on balance, harmony, the mind-body-spirit connection, and interactions with the outside world

Treatments include qi gong, acupuncture, tai chi, massage therapy, food therapy, physical manipulation, and herbal medicine

Limited evidence is available to recommend as a whole medical system

Herbal medications have potential risks, including interactions with prescription medications and contamination of herbal preparations

Box 25.2 • Ayurveda

Distinct paradigm of medicine that originated in India thousands of years ago

Paradigm is based on the theory that everything in the universe is interconnected and all forms of life consist of combinations of 5 energy elements: ether, wind, fire, water, and earth

These 5 elements exist in 3 energetic patterns called *doshas*

When the elements and doshas are in balance, the person is healthy; when unbalanced, the body is weakened and susceptible to illness

Treatments include herbs, certain foods, therapeutic massage, fasting, yoga, and meditation

Limited evidence is available to recommend ayurvedic medicine as a whole medical system

Some ayurvedic supplements have been found to contain lead, mercury, arsenic, or other contaminants

Box 25.3 • Homeopathy

Homeopathy is a whole medical system used for wellness and for prevention and treatment of many diseases

System is based on the concept "like cures like," in which a substance that causes the symptoms of a disease in healthy people can cure similar symptoms in patients who are sick

Practitioners provide medications from natural sources that are serially diluted to levels that no longer have any biologic effect

Research is limited on the overall effectiveness of homeopathy

Risks are generally limited unless patients pursue homeopathy to the exclusion of more proven conventional therapies in the clinical setting of a serious but treatable condition

KEY FACTS

✓ Herbal products from China may be contaminated with heavy metals or pesticides or adulterated with pharmaceuticals

✓ Ayurvedic preparations may contain toxic lead compounds

✓ Most homeopathic products are so diluted that they do not pose a risk unless used to the exclusion of proven conventional therapies

✓ Chiropractic—as effective as conventional treatment of acute low back pain in recent studies

✓ Aggressive cervical spine manipulation may cause vertebral artery dissection with resulting stroke

Mind-Body Medicine

According to the NIH, mind-body medicine focuses on the interactions among the mind, body, and behavior and on the powerful ways in which emotional, mental, social, spiritual, and behavioral factors can affect health directly. Its therapies focus on provision of positive thoughts, emotions, and influences to help promote physical health and help heal the body. In brief, mind-body medicine helps to harness the power of the mind. Therapies include meditation, hypnotherapy, guided imagery, deep breathing, and biofeedback.

Energy Medicine

Energy medicine is based on the belief that imbalances in the energy field of the body result in illness. Its therapies focus on providing and restoring balance of energy to heal the body and promote health. Therapies include acupuncture, therapeutic touch, healing touch, Reiki, and qi gong. In general, treatment of pain through acupuncture has the most evidence and clinical experience to support its use.

Box 25.4 • Chiropractic

Chiropractic focuses on the relationship between the spine and nervous system and its functioning

Chiropractic treatment aims to decrease pain, restore balance, and improve function related to restricted movement in the spine

Chiropractors use their hands to apply a controlled sudden force to correct structural alignment and assist the body in healing

Chiropractors also may use massage, ultrasound therapy, stretching, and electrical muscle stimulation

Evidence shows that chiropractic manipulation can be effective in providing relief from uncomplicated mild to moderate low back pain

Chiropractic manipulation is contraindicated in people with the following conditions:

- Severe osteoporosis
- Previous spinal surgery
- Coagulopathy
- Vertebral instability
- Unstable spine lesions or malignant spinal tumors
- Atherosclerotic disease in the cervical vasculature
- Inflammatory arthritis (eg, rheumatoid arthritis)

Key Definition

Energy medicine: *complementary and alternative medicine therapies that focus on providing and restoring balance of energy to heal the body and promote health.*

Acupuncture

This traditional Chinese medical technique involves the insertion of extremely thin, solid, metallic needles through the skin to various depths at strategic points on the body. Acupuncture aims to restore and maintain health through the stimulation of specific points on the body. No unifying mechanism of action has been identified. An NIH consensus panel in 1997 determined that the evidence of efficacy was sufficient to support the use of acupuncture for 1) postoperative and chemotherapy-related nausea and vomiting in adults and 2) postoperative dental pain. The panel also identified the following as conditions for which acupuncture can be an effective part of an overall treatment strategy: headache, menstrual cramps, tennis elbow, fibromyalgia, myofascial pain, osteoarthritis, and low back pain.

Acupuncture is safe when performed properly, has few adverse effects, and can be useful as a complement to other treatment methods. The most common adverse effects of acupuncture are soreness and mild bleeding or bruising at the needle sites.

Box 25.5 • Massage Therapy

Massage therapy involves manipulation of soft tissue to promote relaxation, ease muscle tension, ease muscle soreness, and decrease stress and anxiety

Massage has many types; common types include Swedish, sports, trigger point, and deep tissue massage

Massage may help to release endorphins, improve circulation, and boost the immune system

This therapy is considered generally safe but may not be appropriate for persons with the following conditions:

- Severe osteoporosis
- Open wounds after surgical procedure
- Bleeding disorders (avoid vigorous massage)
- Burns
- Fractures
- Deep vein thrombosis

KEY FACTS

✓ Massage therapy—shown to be effective in reduction of postsurgical pain and anxiety

✓ Research supports massage as cost-effective treatment for chronic low back pain

✓ Incorporating mind-body medicine into patient care may improve symptoms and promote healing

✓ Acupuncture—the only energy medicine therapy with evidence that supports efficacy

26 Dermatology

CARILYN N. WIELAND, MD

General Dermatology

Skin Cancer

Nonmelanoma skin cancers (eg, basal cell carcinoma, squamous cell carcinoma) are the most common malignancies in the United States. Both basal cell and squamous cell carcinomas most commonly occur on sun-exposed skin. Basal cell carcinoma typically presents as a pearly papule, often with telangiectasias and ulceration (Figure 26.1). It usually grows slowly and is locally invasive, but it may invade vital structures, cause considerable disfigurement, and, rarely, metastasize. In contrast, squamous cell carcinoma has a higher risk of metastases. Squamous cell carcinoma most often presents as a hyperkeratotic or ulcerated papule (Figure 26.2). The following settings pose a high risk of nonmelanoma skin cancer: immunosuppression, irradiated skin, chronic inflammation, and scar. Squamous cell carcinoma is the most common skin cancer in solid organ transplant recipients and is aggressive, with a risk of metastasis of approximately 8%.

Malignant Melanoma

The strongest risk factors for melanoma are a family history of melanoma, numerous nevi, and a previous melanoma. Additional risk factors include fair skin, blond or red hair, sun sensitivity, freckling, intermittent sun exposure, blistering sunburns, immunosuppression, and tanning bed use. Inherited mutations in *CDKN2A* and *CDK4* genes, which have been documented in some families with melanoma, are associated with a 60% to 90% lifetime risk of melanoma. The familial atypical multiple mole melanoma syndrome is transmitted by an autosomal dominant gene.

Central to improved survival with malignant melanoma is early detection and diagnosis. Evaluation for potential melanoma includes inspection for the following morphologic characteristics: *a*symmetry, *b*order irregularity, *c*olor variation, a *d*iameter more than 6 mm, and *e*volution (an **ABCDE evaluation**) (Figure 26.3). Suspicious lesions should be excised for histopathologic review.

Key Definition

ABCDE evaluation: *evaluation for malignant melanoma, including asymmetry, border irregularity, color variation, diameter >6 mm, and evolution.*

Surgical management is recommended for treatment of the primary melanoma and consists of excision with tumor-free margins of 1 to 3 cm. Increase in thickness of a melanoma (Table 26.1) and microscopic ulceration are inversely correlated with survival. In cases with melanoma thickness (Breslow depth) greater than 0.8 mm, sentinel lymph node biopsy can also assist with staging and serve as a prognostic tool. Treatment options for metastatic melanoma include adjuvant high-dose interferon alfa-2b, targeted therapies such as *BRAF* inhibitors, and other immunomodulating therapies.

Cutaneous T-Cell Lymphoma

Cutaneous T-cell lymphoma is a non-Hodgkin lymphoma characterized by expansion of malignant T cells within the skin. The most common clinical presentations are mycosis fungoides and Sézary syndrome. Mycosis fungoides generally presents with discrete or coalescing patches, plaques, or nodules on the skin (Figure 26.4). Mycosis fungoides may progress to involve lymph nodes and viscera. After extracutaneous involvement is recognized, the median duration of survival is about 2.5 years. The course of patients with patch- or plaque-stage cutaneous lesions without extracutaneous disease is less predictable, but

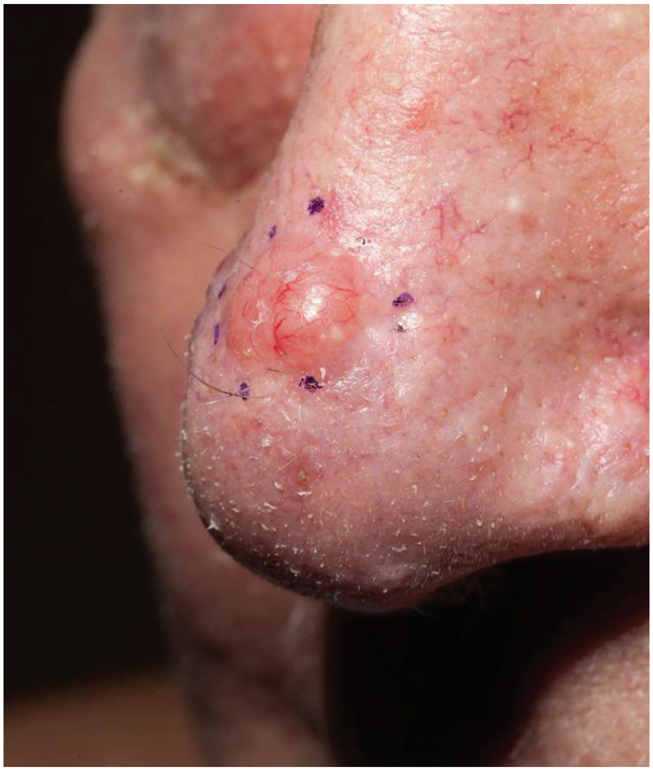


Figure 26.1. *Basal Cell Carcinoma.*

the median duration of survival is approximately 12 years. Sézary syndrome, the more aggressive leukemic form of cutaneous T-cell lymphoma, is characterized by generalized erythroderma, keratoderma of the palms and soles, and a Sézary cell count of more than 1,000/mm^3 in the peripheral blood. Most patients have severe pruritus.

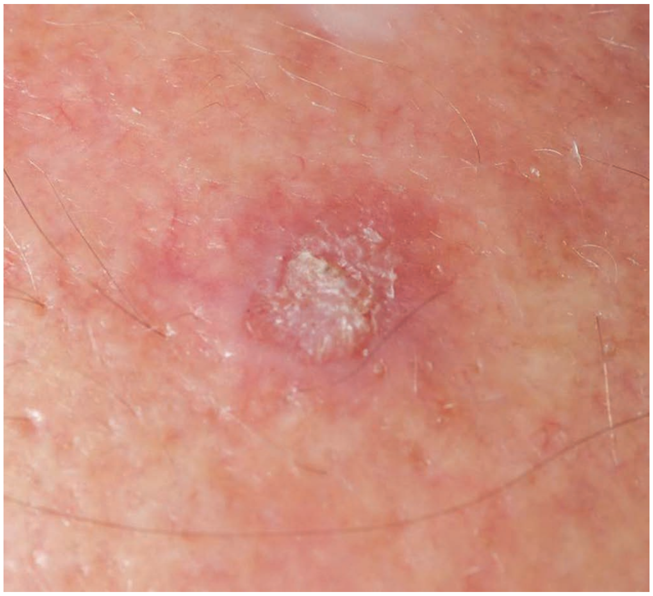


Figure 26.2. *Squamous Cell Carcinoma.*

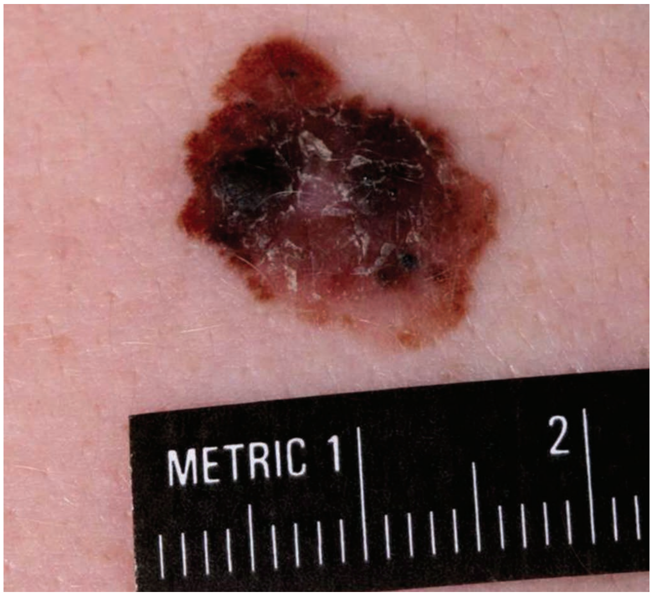


Figure 26.3. *Malignant Melanoma.*

Treatment of cutaneous T-cell lymphoma includes topical corticosteroids, topical nitrogen mustard, psoralen and UV-A (PUVA), radiotherapy (eg, electron beam, orthovoltage), and systemic chemotherapy. Extracorporeal photopheresis, interferons, retinoids, and monoclonal antibodies have also been used.

Psoriasis

Psoriasis is a chronic, inflammatory, multisystem disease that occurs in 2% of the US population. About a third of patients have a family history of psoriasis. Psoriasis commonly presents with discrete red plaques covered with a silvery scale. Patterns of psoriasis include psoriasis vulgaris, which presents with plaques involving the elbows, knees, and scalp (Figure 26.5). Guttate psoriasis is an acute form that often follows streptococcal pharyngitis and presents with small, scaly papules of psoriasis on the trunk and limbs. Other, less common forms of psoriasis include pustular psoriasis, which may be localized to the hands and feet or may be generalized. Approximately 50% of patients with psoriasis have nail abnormalities, most commonly onycholysis, pitting, and oil spots. Lesions of psoriasis may occur at previous

Table 26.1 • Survival in Malignant Melanoma, by Tumor Thickness[a]

Tumor, mm	5-Year Survival, %
<1.0	95.3
1.01-2.00	89.0
2.01-4.00	78.7
>4.00	67.4

[a] No nodal or distant metastasis.

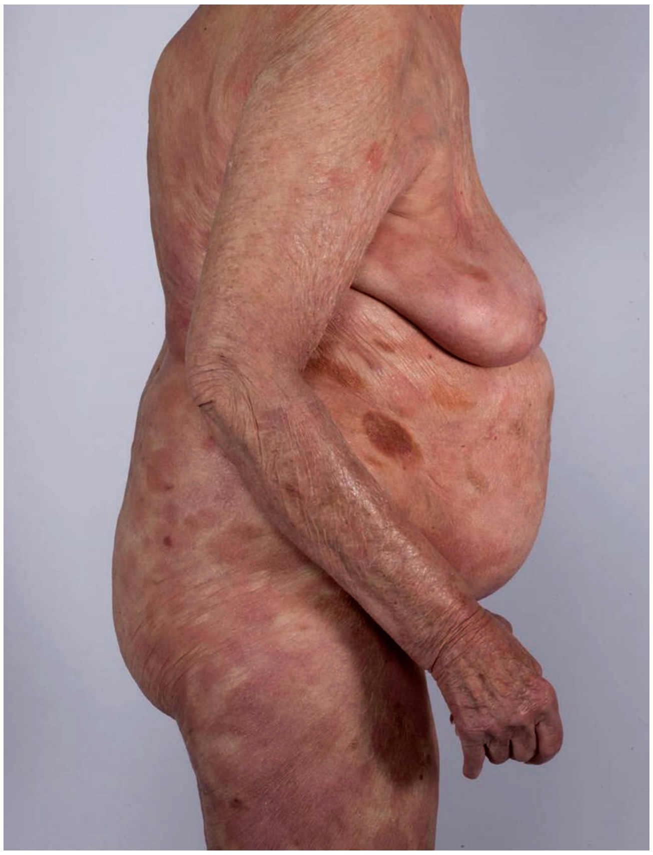


Figure 26.4. *Mycosis Fungoides.*

sites of trauma (koebnerization). Medications such as lithium, β-adrenergic blockers, and antimalarials and discontinuation of the use of systemic corticosteroids can precipitate or exacerbate psoriasis.

Psoriatic arthritis occurs in 5% to 8% of patients with skin psoriasis. An asymmetrical oligoarthritis occurs in 70% of patients with psoriatic arthritis. This group includes patients with “sausage digits” and monarthritis. The second most common presentation is asymmetrical arthritis clinically similar to rheumatoid arthritis, which occurs in 15% of patients with psoriatic arthritis. Distal interphalangeal involvement, arthritis mutilans, and a spinal form of arthritis similar to ankylosing spondylitis each occur in 5% of patients with psoriatic arthritis. Moderate to severe psoriasis has also been associated with obesity and cardiovascular disease.

The treatment of psoriasis includes topical corticosteroids, topical tar preparations, phototherapy, calcipotriene (a topical synthetic vitamin D analogue), and tazarotene (a topical retinoid). Systemic agents used in the treatment of resistant psoriasis include methotrexate, anti–tumor necrosis factor agents (eg, infliximab, etanercept, and adalimumab), anti–interleukin (IL)-12 and IL-23 antibodies (ustekinumab), anti–IL-17 antibodies (eg, secukinumab, ixekizumab, brodalumab), acitretin, and cyclosporine. Systemic therapy should be considered if psoriasis involves a high percentage of cutaneous surface area or psoriatic arthritis is present, or both.

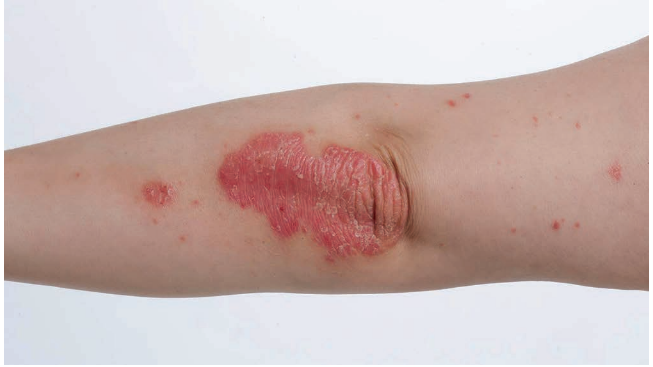


Figure 26.5. *Psoriasis.*

Atopic Dermatitis

Atopy is manifested by atopic dermatitis, asthma, and allergic rhinitis or conjunctivitis. Atopic dermatitis most often presents in infancy and childhood, but flares of dermatitis (or eczema) can occur at any age. Atopic dermatitis classically presents with erythema, lichenification, and crusting of the flexural areas (Figure 26.6).

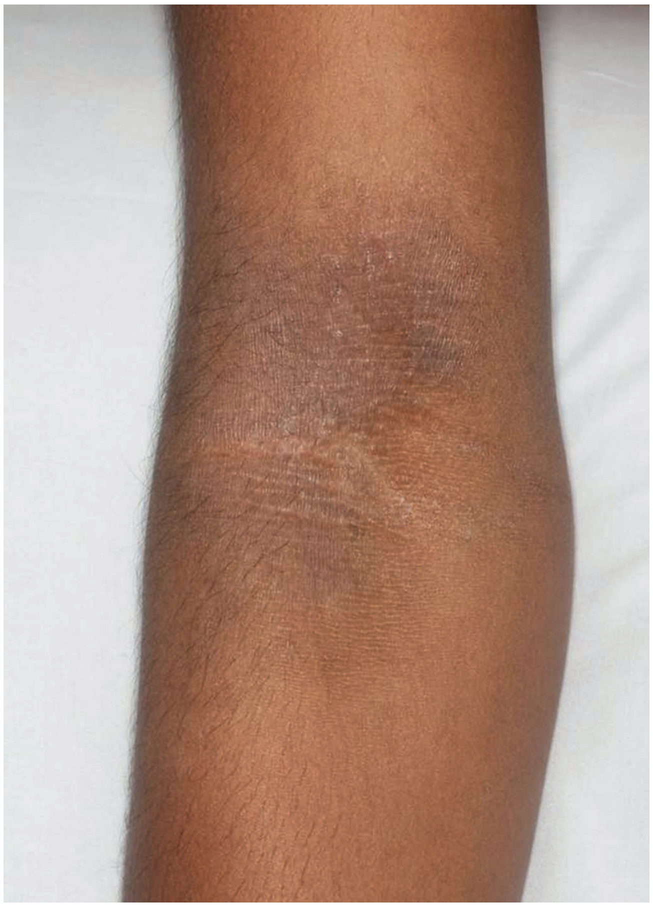


Figure 26.6. *Atopic Dermatitis.*

Disturbances in cell-mediated immunity lead to an increased incidence of bacterial and viral infections. Secondary colonization with *Staphylococcus aureus* presents as a weeping, crusting dermatitis (impetiginization). Eczema herpeticum is a secondary infection with the herpes simplex virus, which may be generalized.

Emollients and topical corticosteroids have been the mainstays of treatment in atopic dermatitis.

Allergic Contact Dermatitis

Allergic contact dermatitis is a form of localized or generalized dermatitis that results from exposure to an antigen. This is a type IV hypersensitivity reaction (delayed and cell-mediated). One must consider the anatomical location of the cutaneous lesions and environmental exposure to allergens, including occupational, household, and recreational contactants, to define the cause of the contact dermatitis. Workers in certain occupations (eg, health care workers, hair stylists) with persistent exposure to antigens over time are at greater risk for contact dermatitis.

Testing to identify specific contact allergens is performed with patch testing. This testing involves the application of substances to a patient's back; each substance is placed under a small aluminum disk covered with adhesive tape. These disks are left on the patient's back for 48 hours, and the results are interpreted at 48 and 96 hours (since it is a delayed hypersensitivity reaction). Positive reactions occur often to the following antigens: nickel sulfate, neomycin sulfate, benzocaine, fragrances, thimerosal, paraphenylenediamine, and formaldehyde.

Nickel sulfate allergies are often associated with inexpensive jewelry, clothing snaps, and belt buckles (Figure 26.7). Neomycin sulfate and benzocaine are components of many topical antimicrobial and analgesic preparations. Thimerosal is a commonly used preservative in contact lens solutions. Paraphenylenediamine is present in hair dyes and other cosmetics; para-aminobenzoic acid in sunscreens is immunologically related to paraphenylenediamine. Formaldehyde is a common preservative in cosmetics and shampoos.

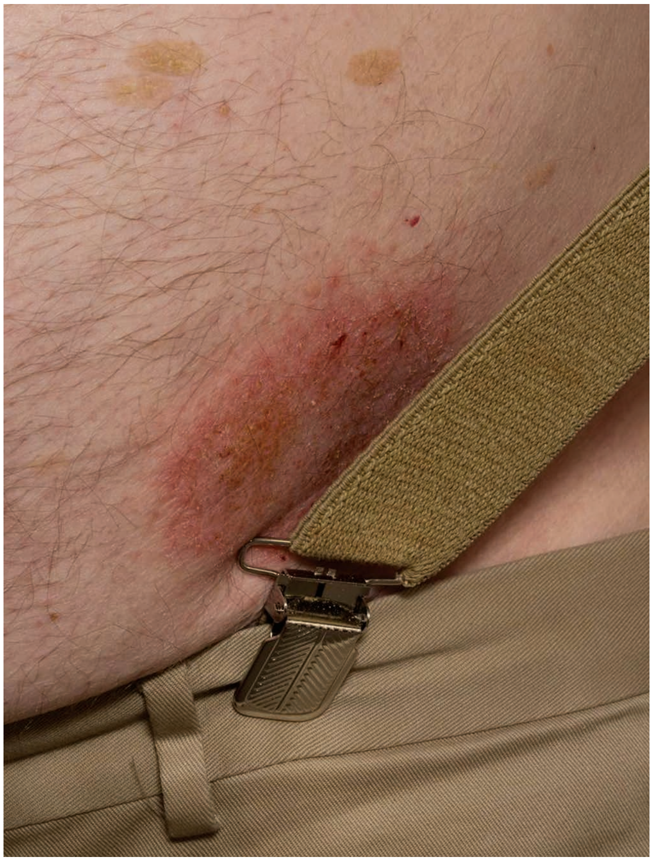


Figure 26.7. *Allergic Contact Dermatitis.*

Acne Vulgaris

Acne occurs physiologically at puberty with varying degrees of severity but may persist into the second and third decades of life. Its pathogenesis is multifactorial; heredity, increase in sebaceous gland activity, hormonal influences, disturbances of keratinization, and bacterial infection have all been implicated. The primary lesions of acne are noninflammatory and include microcomedones, closed comedones (whiteheads), and open comedones (blackheads). The secondary or inflammatory lesions include papules and pustules, nodules, and cysts. Treatment options for acne are listed in Table 26.2.

Isotretinoin (13-*cis*-retinoic acid) is a synthetic vitamin A derivative used primarily for the treatment of severe nodulocystic acne vulgaris. The greatest risk associated with use of systemic retinoids is teratogenicity. Before isotretinoin is prescribed, female patients must be counseled on this adverse effect, and 2 forms of reliable contraception must be used during therapy and for at least 1 month after isotretinoin use is discontinued. The systemic retinoids are associated with various cutaneous adverse effects, including xerosis (dry skin), dermatitis, and cheilitis. Potential laboratory abnormalities include hyperlipidemia, increased liver enzyme levels, and leukopenia. Skeletal hyperostosis may occur, particularly in association with long-term use. Concerns have been raised regarding an association of systemic retinoids with depression, suicidal ideation, and inflammatory bowel disease.

Table 26.2 • Treatment of Acne Vulgaris

Type of Acne	Treatment
Comedonal	Topical tretinoin, benzoyl peroxide
Papular or pustular	Same as above, plus topical or systemic antibiotics
Cystic	Systemic antibiotics; if severe, isotretinoin

KEY FACTS

- ✓ Basal cell carcinoma usually grows slowly and is locally invasive; squamous cell carcinoma is more likely to metastasize
- ✓ Cutaneous T-cell lymphoma—non-Hodgkin lymphoma most commonly presenting as mycosis fungoides or Sézary syndrome
- ✓ Up to 8% of patients with skin psoriasis (red plaques covered with silvery scale) also have psoriatic arthritis (usually asymmetrical oligoarthritis)
- ✓ Atopic dermatitis—most likely to present in infancy and childhood; can flare at any age
- ✓ Acne beginning at puberty—may persist into age 20s and 30s; teratogenicity is greatest risk of systemic retinoid therapy

Autoimmune Bullous Diseases

Autoimmune bullous diseases are a diverse collection of conditions in which autoantibodies target various components of the skin, leading to varying clinical presentations. The diagnosis of autoimmune bullous disease can be aided by skin biopsy for direct immunofluorescence (which shows different patterns of antibody deposition in the skin) and serologic testing for autoantibodies.

Bullous pemphigoid (Figure 26.8) is the most common autoimmune blistering disease. The disease predominantly occurs in elderly patients and usually presents with large, tense bullae on an erythematous base with a predilection for flexural areas. Targeted antigens in bullous pemphigoid include basement membrane proteins, bullous pemphigoid antigen 1 (BP230), and bullous pemphigoid antigen 2 (BP180). Direct immunofluorescence testing shows a linear pattern at the basement membrane. Treatment of bullous pemphigoid includes topical and systemic corticosteroids, tetracyclines, and mycophenolate mofetil and other immunosuppressive agents.

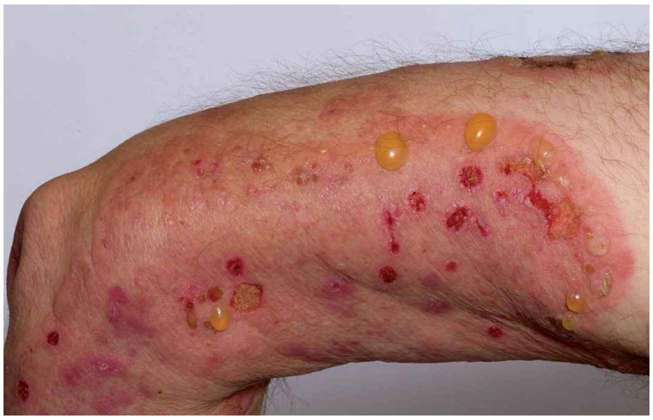


Figure 26.8. *Bullous Pemphigoid.*

Pemphigoid has several other forms. Cicatricial pemphigoid (or mucous membrane pemphigoid) is characterized by mucosal lesions, with limited or no cutaneous lesions. The disease predominantly affects oral and ocular mucous membranes. Often, cyclophosphamide is used, particularly for patients with ocular involvement, because this condition can lead to blindness. Pemphigoid gestationis consists of intensely pruritic urticarial papules, plaques, or blisters, usually occurring in the latter half of pregnancy. The serum of approximately one-half of patients with herpes gestationis contains the HG factor, which is a complement-fixing immunoglobulin (Ig) G anti–basement membrane zone antibody.

Pemphigus vulgaris is typically characterized as oral lesions and more flaccid cutaneous bullae, since the autoantibodies affect more superficial components in the skin—the intercellular proteins called *desmogleins* (Figure 26.9). Direct immunofluorescence testing shows intercellular staining in the epidermis. Rituximab and high-dose corticosteroids generally are required to control pemphigus, but other, corticosteroid-sparing immunosuppressive agents have been used.

Another variant of pemphigus is pemphigus foliaceus; its subsets include pemphigus erythematosus and fogo selvagem, an endemic form of pemphigus that occurs in South America. Pemphigus foliaceus may present with superficial scaling, crusty lesions of the head and neck area (in a seborrheic dermatitis–like pattern) or in a generalized distribution.

Dermatitis herpetiformis (Figure 26.10) is characterized by extremely pruritic, grouped vesicles occurring predominantly over the elbows, knees, buttocks, back of the neck and scalp, and lower part of the back, usually beginning in the third or fourth decade of life. Virtually all patients with dermatitis herpetiformis have some degree of gluten-sensitive enteropathy (celiac sprue),

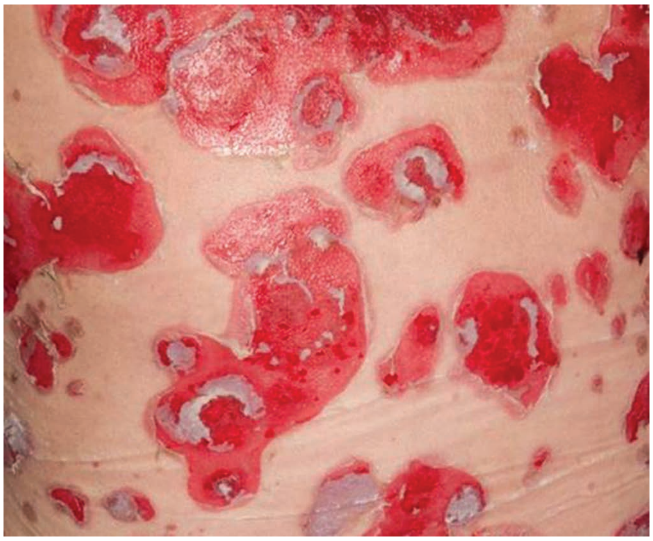


Figure 26.9. *Pemphigus Vulgaris.*

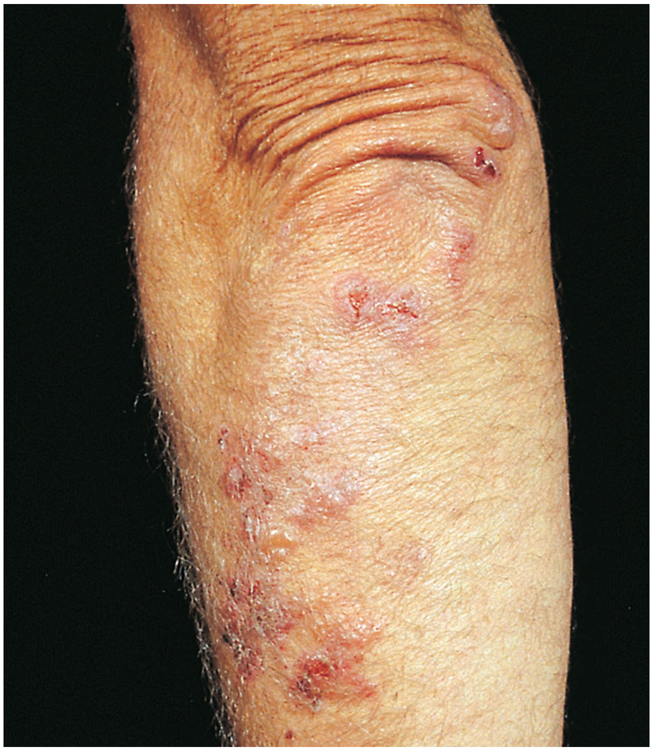


Figure 26.10. *Dermatitis Herpetiformis.*

although it may be subclinical. This association is important, since gluten-sensitive enteropathy is associated with an increased risk of small B-cell lymphoma, and only adherence to a gluten-free diet affects this risk. Testing for tissue transglutaminase or endomysial antibodies is useful for both diagnosis and management of dermatitis herpetiformis, although these antibodies correlate with the degree of gluten-sensitive enteropathy rather than the skin lesions per se. The mainstays of treatment of dermatitis herpetiformis are dapsone and a gluten-free diet. Patients who strictly adhere to a gluten-free diet may have a decreased need for dapsone.

Linear IgA bullous dermatosis is characterized by vesicles or blisters on an erythematous base in a generalized distribution with a high rate of mucosal involvement. Drug-induced disease has occurred with vancomycin treatment.

Erythema Multiforme

Erythema multiforme (Figure 26.11) is an acute, usually self-limited eruption of typically targetoid plaques. It often presents on the palms and lips. A subset of patients with erythema multiforme may have recurrent lesions. When erythema multiforme presents with mucosal and cutaneous lesions, it is referred to as *Stevens-Johnson syndrome*. Various etiologic factors have been implicated in erythema multiforme. The most commonly cited precipitating factor is viral infection, particularly herpes simplex virus. Infection with herpes simplex virus is responsible for a considerable percentage of cases of recurrent erythema multiforme. Other infectious agents that have been noted to cause erythema multiforme include *Mycoplasma pneumoniae* and *Yersinia enterocolitica*. Use of certain drugs has been reported to induce erythema multiforme, particularly sulfonamides, barbiturates, and anticonvulsants.

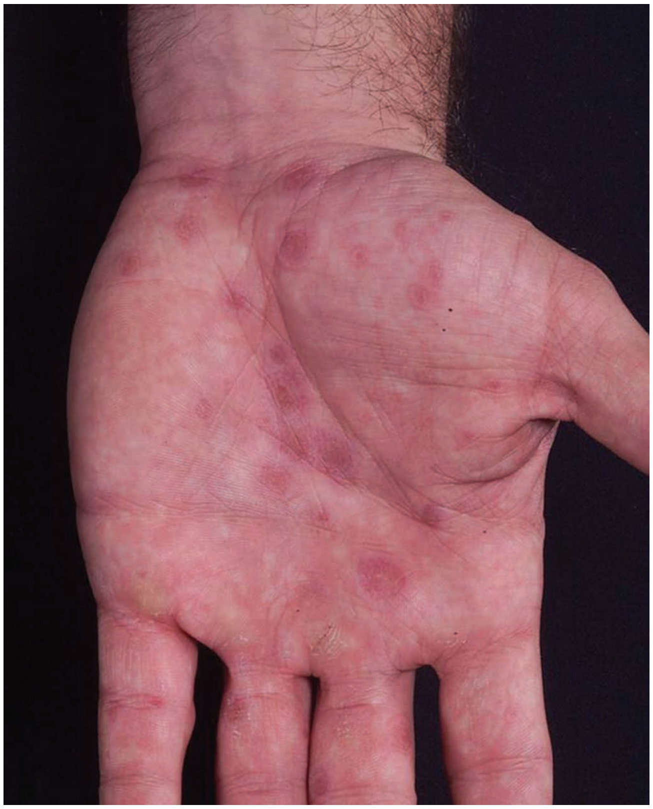


Figure 26.11. *Erythema Multiforme.*

Lichen Planus

Lichen planus typically presents as polygonal, violaceous, flat-topped papules or plaques on the wrists and ankles (Figure 26.12). The lesions are very pruritic. A characteristic feature

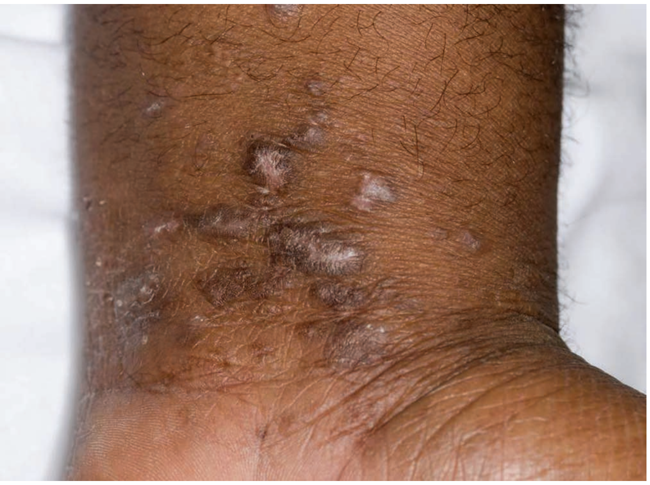


Figure 26.12. *Lichen Planus.*

is fine, reticulated, whitish lines visible on top of the lesions, known as *Wickham striae*. Various forms of lichen planus can affect the oral and genital mucosa, nails, or scalp. Oral lichen planus can be ulcerative and may extend to esophageal involvement.

Erythema Nodosum

Erythema nodosum (Figure 26.13) typically presents as tender, erythematous, subcutaneous nodules localized to the pretibial areas. The nodules may be acute and self-limited or chronic, lasting for months to years. The most common cause is streptococcal pharyngitis. Other infectious agents that have been implicated in the development of erythema nodosum include *Y enterocolitica, Coccidioides*, and *Histoplasma*. Drug-induced erythema nodosum most often is associated with oral contraceptives and sulfonamides. Other associations with erythema nodosum include sarcoidosis, inflammatory bowel disease, and Behçet syndrome.

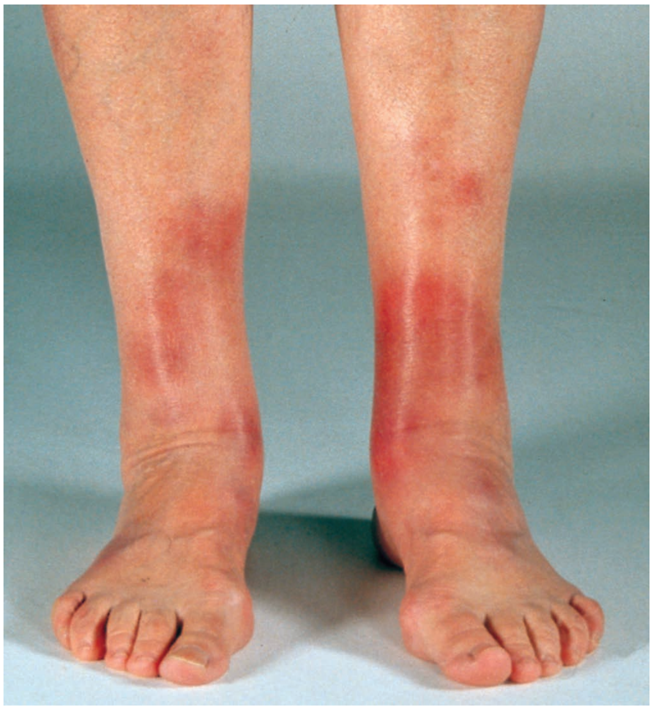


Figure 26.13. *Erythema Nodosum.*

KEY FACTS

- ✓ Bullous pemphigoid—most common autoimmune blistering disease, with large, tense bullae on erythematous base favoring flexural areas
- ✓ Pemphigus vulgaris—autoimmune blistering disease with oral lesions and more flaccid cutaneous bullae
- ✓ Dermatitis herpetiformis—very pruritic, grouped vesicles over elbows, knees, buttocks, back of neck and scalp, lower back; associated with gluten sensitivity
- ✓ Erythema multiforme—most commonly caused by viral infection, particularly herpes simplex; also caused by other infectious agents, and drugs
- ✓ Erythema nodosum—most commonly caused by streptococcal pharyngitis; also caused by other infectious agents and, drug use; associated with sarcoidosis, inflammatory bowel disease, Behçet syndrome

Drug Reactions

The morphologic spectrum of reactions that may be induced by medications is broad, and many different medications may produce a given cutaneous reaction. Types of cutaneous lesions induced by drugs include maculopapular eruptions, acne, folliculitis, necrotizing vasculitis, vesiculobullous lesions, erythema multiforme, erythema nodosum, fixed drug eruptions, lichenoid reactions, photosensitivity reactions, pigmentary changes, and hair loss. The most common types of clinical presentations (in descending order of frequency) are exanthematous or morbilliform eruptions, urticaria or angioedema, fixed drug eruptions, and erythema multiforme. Stevens-Johnson syndrome, toxic epidermal necrolysis (diffuse skin sloughing), exfoliative erythroderma, and photosensitive eruptions are less common. Table 26.3 outlines the types of cutaneous reactions to drugs.

Exanthematous or morbilliform eruptions are the most common type of cutaneous drug reaction. This type of eruption usually begins within a week of therapy onset, but it may occur more than 2 weeks after initiation of the therapy or up to 2 weeks after use of the drug has been discontinued. Ampicillin, penicillin, and cephalosporins are commonly associated with morbilliform eruptions. A fixed drug eruption is 1 or several lesions that recur at the same anatomical location on rechallenge with the medication. The genital and facial areas are common

Table 26.3 • Cutaneous Reactions to Drugs

Type of Skin Reaction	Cause
Urticarial	Aspirin, penicillin, blood products
Photoallergic	Sulfonamides, thiazides, griseofulvin, phenothiazines
Phototoxic	Tetracyclines
Slate-gray discoloration	Chlorpromazine
Slate-blue discoloration	Amiodarone
Yellow or blue-gray pigmentation	Antimalarials

sites of involvement. Phenolphthalein, barbiturates, salicylates, and oral contraceptives have been implicated in causing fixed drug eruptions. Lichenoid drug eruptions are morphologically similar to lichen planus (with violaceous papules of the skin), and most often have been associated with gold and antimalarial drugs. Yet, various medications may induce this type of reaction.

Cutaneous Signs of Underlying Malignancy

Cutaneous metastasis occurs in 1% to 5% of patients with metastatic neoplasms. The types of neoplasms metastatic to the skin are lung, breast, kidney, gastrointestinal tract, melanoma, and ovary. Lesions usually present on the scalp, face, or trunk.

Paget disease of the nipple is an erythematous, scaly, or weeping eczematous eruption of the areola. Virtually all patients with Paget disease have an underlying ductal carcinoma of the breast. In contrast, extramammary Paget disease, a morphologically similar eruption that usually occurs in the anogenital region, is associated with underlying carcinoma in only about 50% of cases. Extramammary Paget disease may be associated with underlying cutaneous adnexal carcinoma or with underlying visceral carcinoma (particularly of the genitourinary or distal gastrointestinal tract).

Acanthosis nigricans (Figure 26.14) consists of velvety brown plaques of the intertriginous regions, particularly the axillae and groin. It most commonly occurs with obesity and type 2 diabetes, but a sudden or diffuse presentation in an atypical clinical setting may be associated with adenocarcinoma of the gastrointestinal tract, particularly the stomach.

Pyoderma gangrenosum (Figure 26.15) consists of ulcers with undermined, inflammatory, violaceous borders that heal with cribriform scarring. The lesions are most commonly associated with inflammatory bowel disease or rheumatoid arthritis. The occurrence of the disease at sites of trauma (pathergy) is classic. Pyoderma gangrenosum may be associated with malignancy of the hematopoietic system, particularly leukemia.

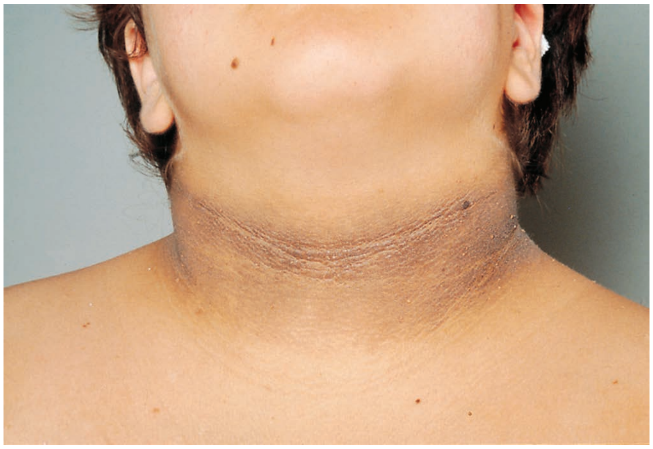


Figure 26.14. *Acanthosis Nigricans.*

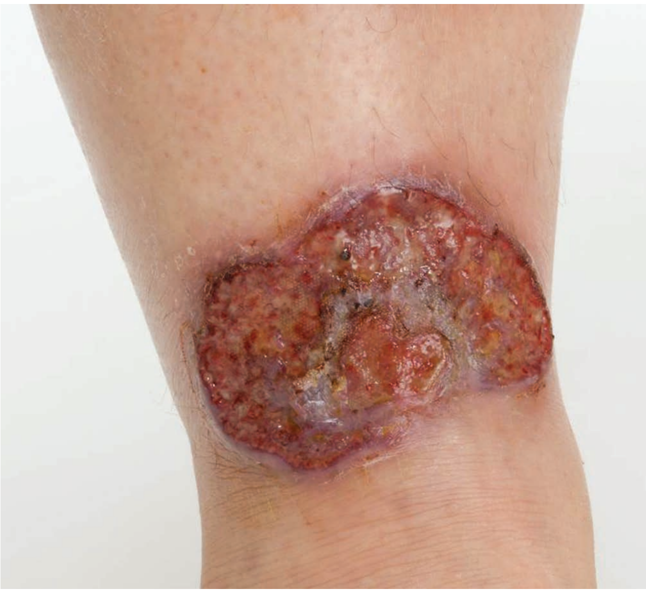


Figure 26.15. *Pyoderma Gangrenosum.*

The skin lesions of glucagonoma syndrome (necrolytic migratory erythema) (Figure 26.16) consist of erosions, crusting, and peeling involving the perineum and perioral areas, but they may be generalized. The syndrome also includes stomatitis, glossitis (beefy tongue), anemia, diarrhea, and weight loss. It is associated with an islet cell (α) tumor of the pancreas.

Gardner syndrome is a hereditary (autosomal dominant) form of colon polyposis. Cutaneous clinical features include soft-tissue tumors (dermoids, lipomas, and fibromas) and sebaceous (epidermal inclusion) cysts of the face and scalp. It is associated with a high incidence of colon carcinoma. Malignant tumors of other sites, including adrenal gland, ovary, and thyroid, have also been associated with this syndrome.

Hirsutism may reflect androgen excess due to an adrenal or ovarian tumor, but hypertrichosis is an increase in hair unrelated

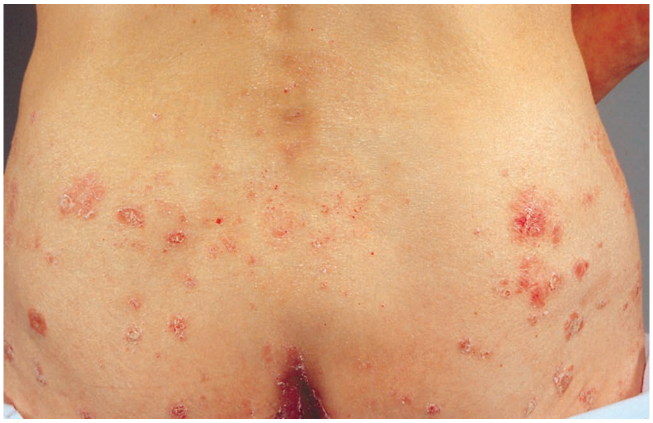


Figure 26.16. *Glucagonoma Syndrome (Necrolytic Migratory Erythema).*

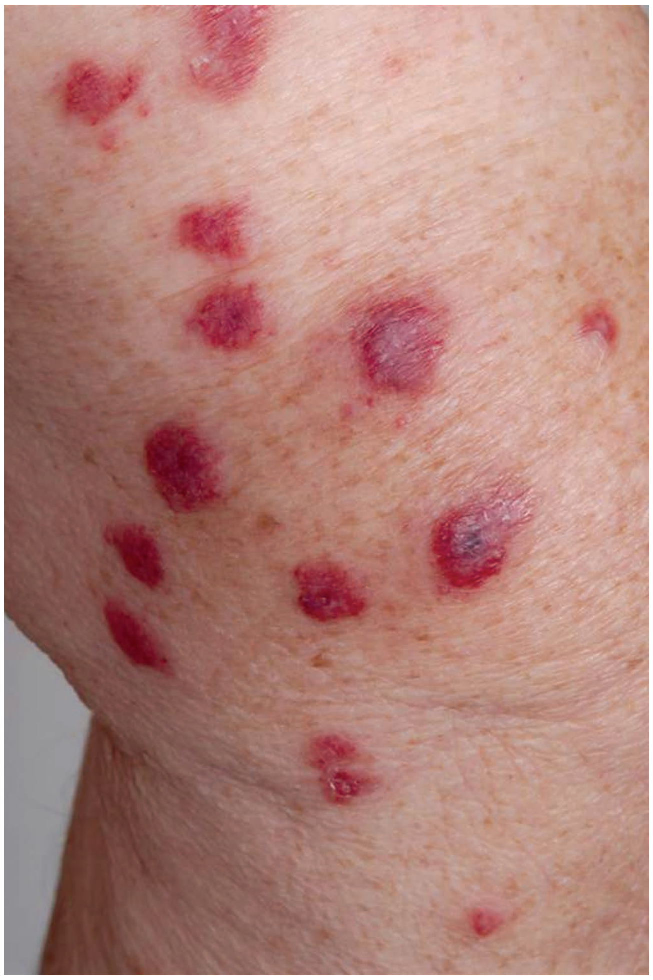


Figure 26.17. *Sweet Syndrome.*

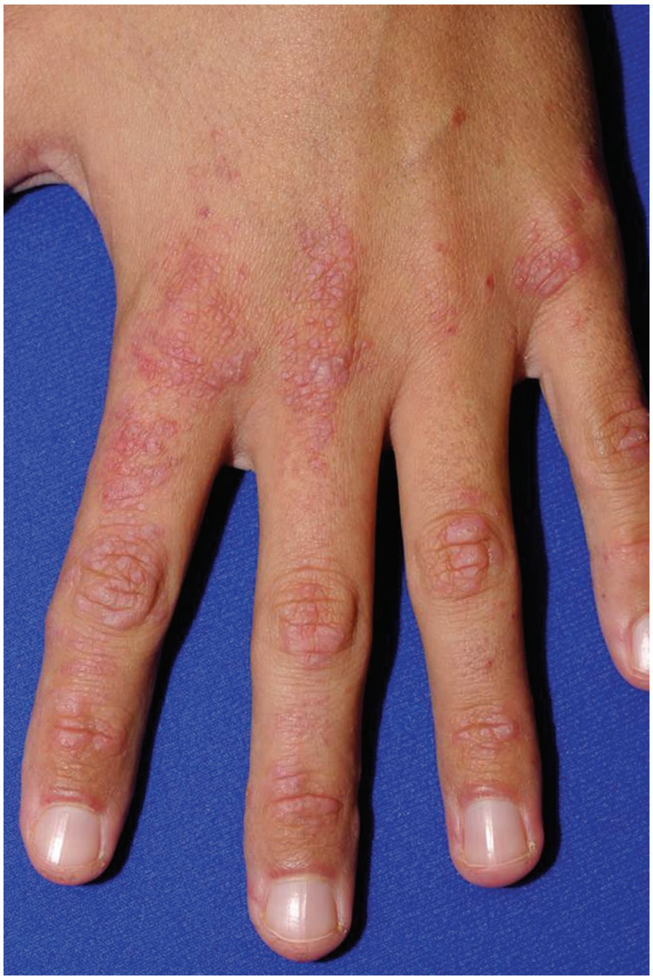


Figure 26.18. *Dermatomyositis: Gottron Papules.*

to androgen excess, such as hypertrichosis lanuginosa acquisita (growth of soft downy hair). It has been associated with carcinoid tumor, adenocarcinoma of the breast, lymphoma, gastrointestinal tract tumors, and other types of neoplasms.

The skin lesions of Sweet syndrome (an acute febrile neutrophilic dermatosis) consist of reddish plaques and nodules, most commonly located on the proximal aspects of the extremities and face (Figure 26.17). The syndrome is associated with leukemia, particularly acute myelocytic or acute myelomonocytic leukemia, although many other disease associations also have been noted.

Generalized pruritus is the presentation for many cutaneous and systemic disorders. Pruritus may be the presenting symptom in lymphoma.

In dermatomyositis, the pathognomonic skin lesions are Gottron papules (Figure 26.18) involving the skin over the joints of the fingers, elbows, and knees. Poikilodermatous lesions or erythematous maculopapular eruptions may involve the face diffusely, particularly the periorbital area (heliotrope rash [Figure 26.19]), trunk, and extremities. The cutaneous lesions are photosensitive and pruritic. Dermatomyositis is characterized by proximal myositis. The disease is associated with an increased incidence of underlying malignancy, especially ovarian cancer.

Amyloidosis may present clinically as macroglossia (Figure 26.20), waxy papules on the eyelids or nasolabial folds, pinch purpura, and postproctoscopic purpura (Figure 26.21). Amyloidosis may be associated with multiple myeloma.

Tylosis is a rare disorder characterized by palmar-plantar keratoderma associated with esophageal carcinoma. It has autosomal dominant inheritance.

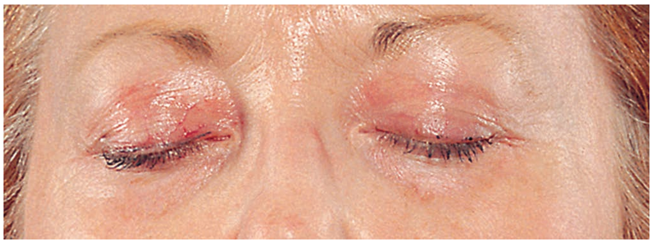


Figure 26.19. *Dermatomyositis: Heliotrope Discoloration.*

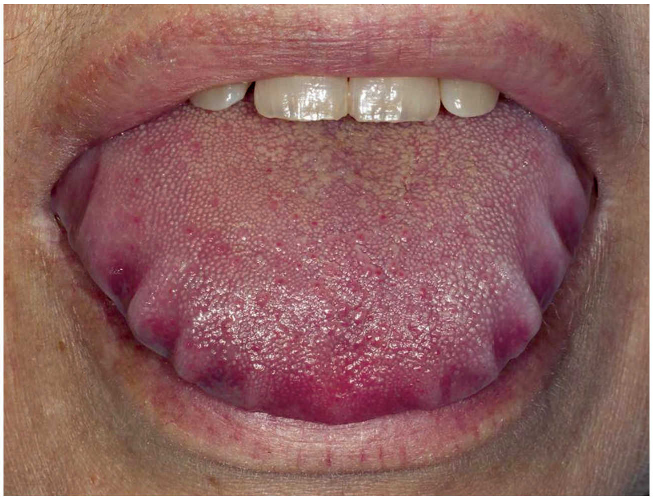


Figure 26.20. Amyloidosis: Macroglossia.

KEY FACTS

- ✓ Exanthematous or morbilliform eruptions—most common type of cutaneous drug reaction
- ✓ Metastatic neoplasms (lung, breast, kidney, gastrointestinal tract, melanoma, and ovary)—spread to skin in 1%-5% of patients
- ✓ Acanthosis nigricans—most common with obesity and type 2 diabetes; may be associated with gastrointestinal tract adenocarcinoma
- ✓ Pyoderma gangrenosum—most common with inflammatory bowel disease and rheumatoid arthritis; may be associated with leukemia
- ✓ Dermatomyositis—associated with increased incidence of underlying cancer, especially ovarian cancer

Dermatology: An Internist's Perspective

Pulmonary

The skin is involved in sarcoidosis for 15% to 35% of patients. Lesions may present as 1) lupus pernio (red swelling of the nose), 2) translucent papules around the eyes and nasolabial folds, 3) annular lesions with central atrophy, 4) nodules on the trunk and extremities, and 5) scar involvement of sarcoidosis (Figure 26.22). Acute sarcoidosis may present with a combination of erythema nodosum, bilateral hilar lymphadenopathy, fever, and arthralgias (Löfgren syndrome). Erythema nodosum is discussed in more detail earlier in this chapter.

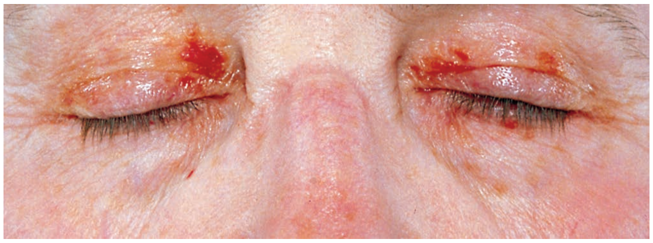


Figure 26.21. Amyloidosis: Postproctoscopic Purpura.

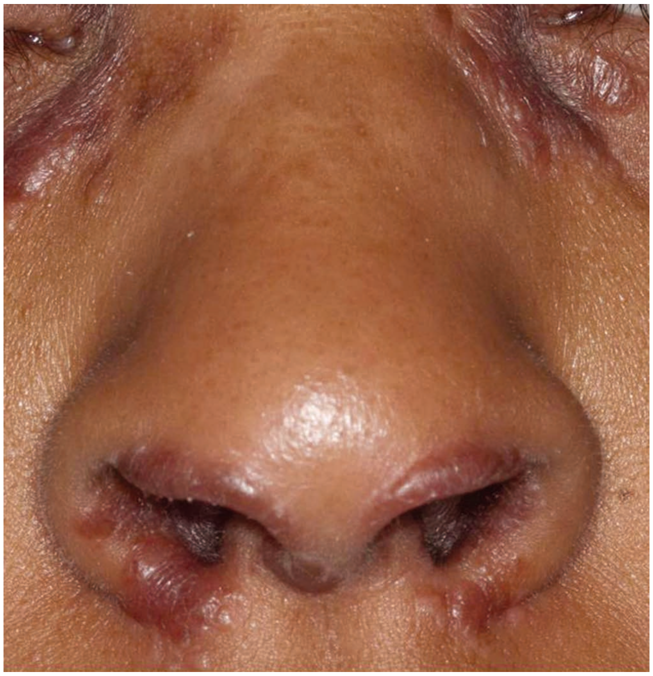


Figure 26.22. Sarcoidosis.

In antineutrophil cytoplasmic autoantibody–associated granulomatous vasculitis, cutaneous involvement occurs in more than 50% of patients and is manifested by cutaneous infarction, ulceration, hemorrhagic bullae, purpuric papules, or urticaria. A skin biopsy may show hypersensitivity vasculitis or granulomatous vasculitis.

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) is characterized by a combination of adult-onset asthma, peripheral eosinophilia, and pulmonary involvement with recurrent pneumonia or transient infiltrates. Skin lesions have been reported in up to 60% of patients and consist of palpable purpura, cutaneous infarcts, and subcutaneous nodules.

In relapsing polychondritis, episodic destructive inflammation occurs in cartilage of the ears, nose, and upper airways. Associated arthritis and ocular involvement may develop. In the acute stage, the ears may be red, swollen, and tender. Later, the ears become soft and flabby. Nasal chondritis may lead to saddle-nose deformities. Relapsing polychondritis is mediated by antibodies to type II collagen.

Cardiovascular

Pseudoxanthoma elasticum may be transmitted by autosomal dominant or autosomal recessive inheritance. Yellow xanthomalike papules (so-called plucked-chicken skin) occur on the neck, axillae, groin, and abdomen. Angioid streaks (tears in Bruch membrane of the eye) can contribute to vision loss. Skin biopsy shows degeneration of elastic fibers. Systemic associations include stroke, myocardial infarction, peripheral vascular disease, and gastrointestinal tract hemorrhage.

Ehlers-Danlos syndrome involves 10 subgroups that differ in severity and systemic associations. Cutaneous findings are skin hyperextensibility with hypermobile joints and "fish mouth" type scars. Ehlers-Danlos syndrome is associated with angina, peripheral vascular disease, and gastrointestinal tract bleeding.

Erythema marginatum is one of the diagnostic criteria for acute rheumatic fever. This uncommon eruption occurs on the trunk and is characterized by erythematous plaques with rapidly mobile serpiginous borders.

Gastrointestinal Tract

Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia), an autosomal dominant disorder, is manifested by cutaneous and mucosal telangiectasias. Frequent nosebleeds and gastrointestinal tract bleeds may be a presenting feature. Pulmonary arteriovenous malformations and central nervous system angiomas are also characteristics of this syndrome.

Acrodermatitis enteropathica is an inherited (autosomal recessive) or acquired disease characterized by zinc deficiency (ie, failure to absorb or failure to supplement zinc). The clinical features include angular cheilitis, a seborrheic dermatitis–like eruption, erosions, blisters, and pustules, with skin lesions involving particularly the face, hands, feet, and perineum. Alopecia and diarrhea are other features of this syndrome.

Peutz-Jeghers syndrome is an inherited (autosomal dominant) syndrome of intestinal polyposis. Patients have hamartomas that mostly involve the small bowel and have a slightly increased risk of carcinoma. Cutaneous lesions include macular pigmentation (freckles) of the lips, periungual skin, fingers, and toes and pigmentation of the oral mucosa.

Cutaneous Crohn disease may present as skin nodules with granulomatous histologic findings. Other manifestations include pyostomatitis vegetans (granulomatous inflammation of the gingivae), granulomatous cheilitis, oral aphthous ulceration, perianal skin tags, perianal fistulas, and peristomal pyoderma gangrenosum.

Dermatitis herpetiformis, pyoderma gangrenosum, Gardner syndrome, and glucagonoma syndrome are described earlier in this chapter.

Nephrologic

Partial lipodystrophy is associated with C3 deficiency and the nephrotic syndrome. Uremic pruritus is associated with end-stage renal disease and responds to UV-B therapy.

Neurocutaneous

Fabry disease is an X-linked recessive disorder due to deficiency of the enzyme α-galactosidase A. The skin changes consist of numerous small vascular tumors (angiokeratomas) in a "bathing suit" distribution that develop during childhood and adolescence. Corneal opacities are present in 90% of patients. Systemic manifestations include paresthesias and pain due to involved peripheral nerves, renal insufficiency, and vascular insufficiency of the coronary and central nervous system.

The clinical features of ataxia-telangiectasia include cutaneous and ocular telangiectasia, cerebellar ataxia, choreoathetosis, IgA deficiency, and recurrent pulmonary infections.

Tuberous sclerosis may be inherited in an autosomal dominant pattern (25%) or may occur sporadically (new mutation). Predominant cutaneous lesions include hypopigmented macules, adenoma sebaceum, subungual or periungual fibromas, and shagreen patch (connective tissue nevus) (Figure 26.23). This syndrome is associated with epilepsy (80%) and intellectual disability (60%). Rhabdomyomas may occur in the heart during

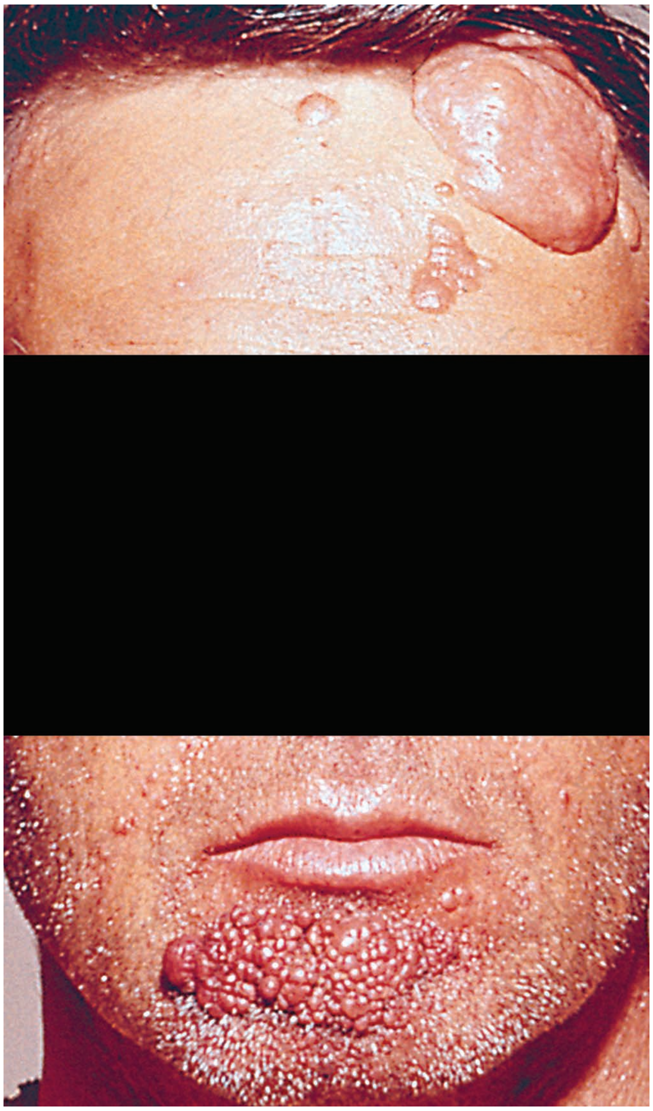


Figure 26.23. *Tuberous Sclerosis: Adenoma Sebaceum and Forehead Plaque.*

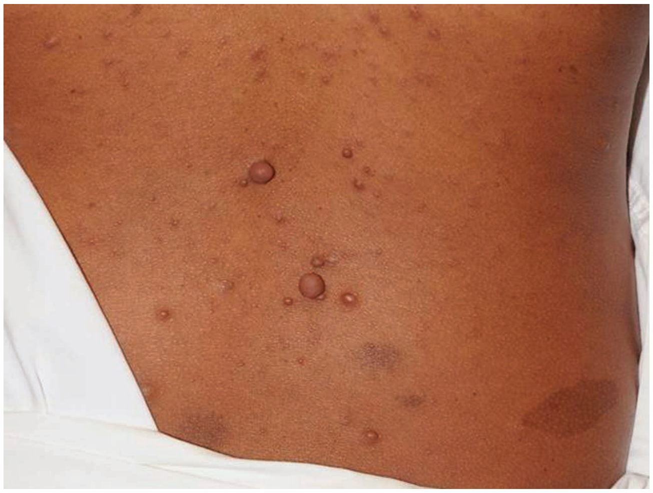


Figure 26.24. *Neurofibromatosis: Multiple Neurofibromas and Café au Lait Macule.*

childhood. Angiomyolipomas occur in the kidneys in up to 80% of adults with this syndrome.

Neurofibromatosis (von Recklinghausen disease) (Figure 26.24) presents with the following skin findings: café au lait spots, axillary freckling (Crowe sign), neurofibromas, and Lisch nodules of the iris. Inheritance is autosomal dominant, and approximately 50% of cases are new mutations. The associated central nervous system tumors include acoustic neuromas, optic gliomas, and meningiomas. Other associated tumors include pheochromocytoma, neuroblastoma, and Wilms tumor. Of note, café au lait spots and neurofibromas frequently occur in the absence of neurofibromatosis. The diagnostic criteria for neurofibromatosis are given in Box 26.1.

Box 26.1 • Criteria for Diagnosis of Neurofibromatosis[a]

1. Six or more café au lait macules >0.5 cm in greatest diameter in prepubertal patients, or >1.5 cm in diameter in adults
2. Two or more neurofibromas of any type, or 1 plexiform neurofibroma
3. Freckling of skin in axillary or inguinal regions
4. Optic gliomas
5. Lisch nodules
6. Osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudarthrosis
7. First-degree relative with neurofibromatosis that meets the above diagnostic criteria

[a] Two or more criteria must be present for diagnosis.

From Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. Arch Neurol. 1988 May;45(5):575-8; used with permission.

Sturge-Weber-Dimitri syndrome is characterized by capillary angioma (port-wine stain) in the distribution of the upper or middle branch of the trigeminal nerve. Associated meningeal angioma may be present in the same distribution. Intracranial tramline calcification, intellectual disability, epilepsy, contralateral hemiparesis, and visual impairment may be associated.

KEY FACTS

- ✓ Up to 60% of patients with Churg-Strauss granulomatosis may have skin lesions (eg, palpable purpura, cutaneous infarcts, subcutaneous nodules)
- ✓ Relapsing polychondritis—episodic inflammation that destroys cartilage of ears, nose, upper airways
- ✓ Osler-Weber-Rendu syndrome—autosomal dominant disorder manifested by cutaneous and mucosal telangiectasias
- ✓ Skin changes of Fabry disease (X-linked recessive disorder due to α-galactosidase A deficiency)—numerous small vascular tumors in "bathing suit" distribution
- ✓ Neurofibromatosis skin findings—café au lait spots, axillary freckling, neurofibromas, and Lisch nodules of iris

Rheumatologic

The skin manifestations of lupus erythematosus (LE) can be classified into acute cutaneous LE (malar rash, generalized photosensitive dermatitis, or bullous LE), subacute cutaneous LE (annular or papulosquamous variants), and chronic cutaneous LE (localized discoid LE, generalized discoid LE, lupus panniculitis, tumid lupus, or chilblain lupus).

Skin lesions are present in up to 85% of patients with acute systemic LE. A butterfly rash with erythema involving the nose and cheeks is characteristic. Erythematous papules and plaques also may occur on the dorsal aspect of the hands, with sparing of the skin overlying the interphalangeal and metacarpal phalangeal joints. Maculopapular erythema also may occur on sun-exposed areas.

Subacute cutaneous LE (Figure 26.25) usually presents with generalized annular plaques often prominent on the upper part of the chest, back, and arms. Subacute cutaneous LE is characterized by the presence of anti-Ro (anti-SSA) antibodies in serum and photosensitivity. In the majority of cases, subacute cutaneous LE is not associated with systemic LE. Treatment is with photoprotection, topical corticosteroids, and hydroxychloroquine.

Discoid LE (Figure 26.26) is characterized by erythematous plaques with follicular hyperkeratosis and scale. It commonly affects the face, scalp, and ears and causes scarring. Although most patients with discoid LE lack manifestations of systemic

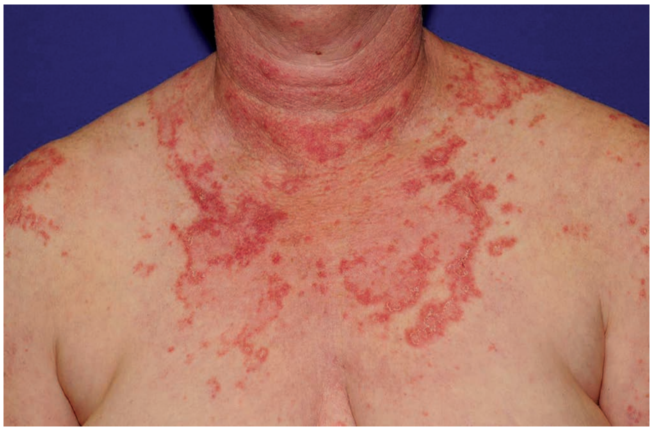


Figure 26.25. *Subacute Cutaneous Lupus Erythematosus.*

LE, approximately 25% of patients with systemic LE have had cutaneous lesions of discoid LE at some point during the course of their illness. Circulating antinuclear antibodies are demonstrable in most patients with systemic LE and subacute cutaneous LE, but they are present in only a small percentage of patients with discoid LE.

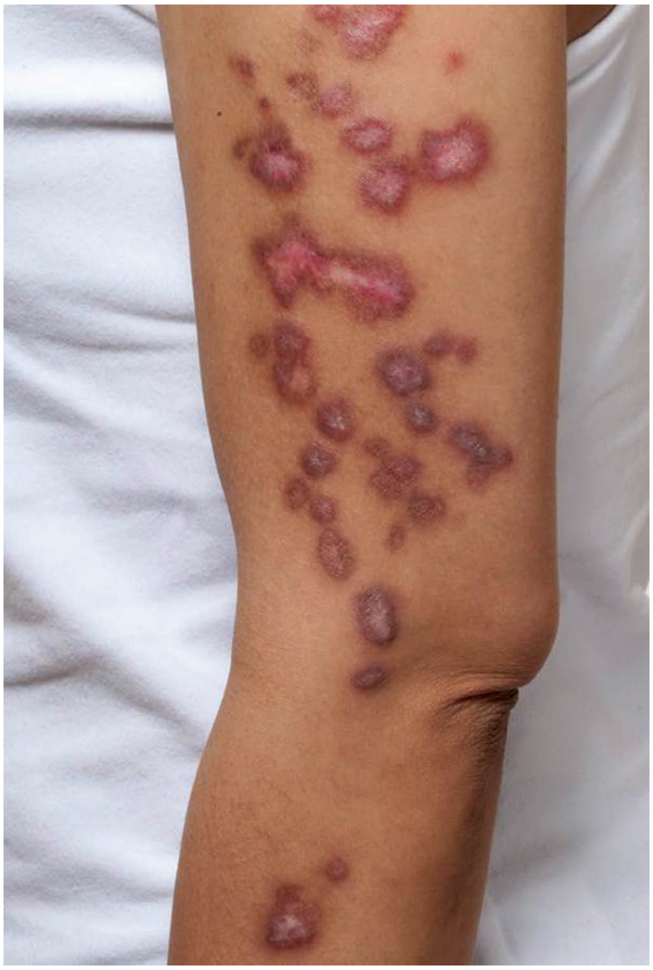


Figure 26.26. *Discoid Lupus Erythematosus.*

The term *scleroderma* encompasses a wide spectrum of diseases, ranging from generalized multisystem disease to localized cutaneous disease. The systemic end of the spectrum is represented by diffuse scleroderma and the CREST (*c*alcinosis cutis, *R*aynaud phenomenon, *e*sophageal involvement, *s*clerodactyly, and *t*elangiectasia) syndrome. The middle area of the spectrum is represented by eosinophilic fasciitis and linear scleroderma, which may have systemic involvement. Localized scleroderma (also known as *morphea*) may be a single plaque or may be multiple plaques in a generalized distribution.

Systemic scleroderma consists of diffuse sclerosis associated with smoothness and hardening of the skin, with a masklike face and microstomia. Sclerodactyly, periungual telangiectasia, telangiectatic mats, hyperpigmentation, and cutaneous calcification may be observed. Esophageal, pulmonary, renal, and cardiac involvement may be associated with systemic scleroderma. The CREST syndrome (Figure 26.27) is associated with circulating anticentromere antibodies.

Eosinophilic fasciitis manifests as tightly bound thickening of the skin and underlying soft tissues of the extremities. Other features include arthralgias, hypergammaglobulinemia, and peripheral blood eosinophilia.

Morphea manifests as discrete sclerotic plaques with a white shiny center and erythematous or violaceous periphery (Figure 26.28). Localized or linear scleroderma may have various presentations depending on extent, location, and depth of sclerosis. Most lesions are characterized by sclerosis and atrophy associated with depression or delling of the soft tissue; underlying bone may be affected in linear scleroderma.

In rheumatoid arthritis, rheumatoid nodules may occur over the extensor surfaces of joints, most commonly on the dorsal aspects of the hands and elbows. Rheumatoid vasculitis with

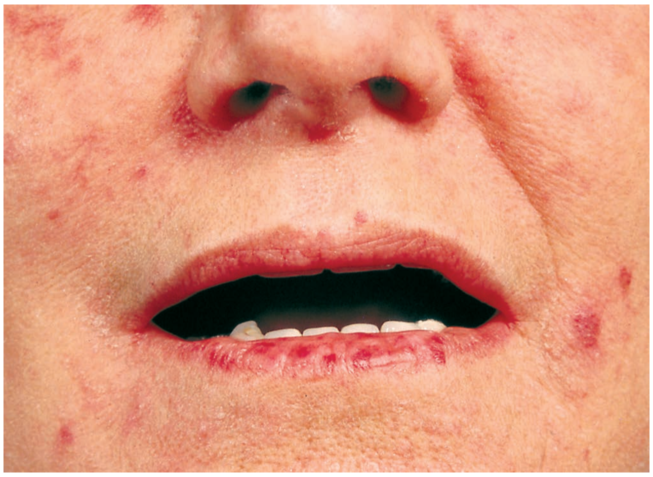


Figure 26.27. *Scleroderma: CREST (Calcinosis Cutis,* R*aynaud Phenomenon,* E*sophageal Involvement,* S*clerodactyly, and* T*elangiectasia) Syndrome.*

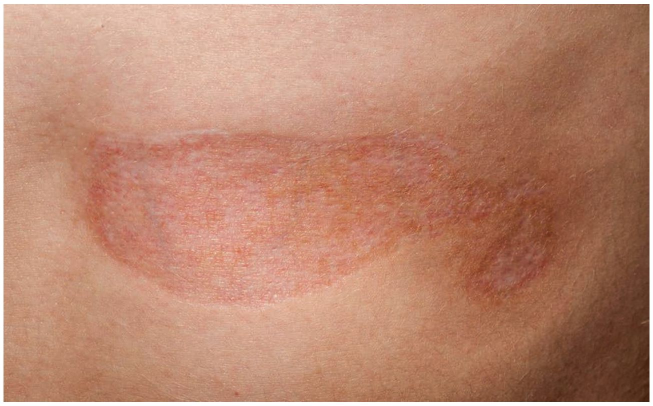


Figure 26.28. Morphea.

ulceration may occur in the clinical setting of rheumatoid arthritis with a high circulating rheumatoid factor level.

Reactive arthritis consists of the triad of urethritis, conjunctivitis, and arthritis. The disease usually affects young men. Two-thirds of patients have skin lesions—namely, circinate balanitis (erythematous plaques of the penis) and keratoderma blennorrhagicum (pustular psoriasiform eruption of the palms and soles). Most patients test positive for HLA-B27.

Erythema migrans is an annular, sometimes urticarial, erythematous plaque presenting as a manifestation of Lyme disease. The plaque develops subsequent to a tick bite. The deer tick *Ixodes scapularis* contains the spirochete *Borrelia burgdorferi*, which is responsible for the erythema migrans. Only 25% of patients recall tick bite. Other acute features of Lyme disease include fever, headaches, myalgias, arthralgias, and lymphadenopathy. Arthritis is a late complication of Lyme disease. Weeks or months after the initial Lyme disease illness, meningoencephalitis, peripheral neuropathy, myocarditis, atrioventricular node block, or destructive erosive arthritis may develop.

Key Definition

Erythema migrans: *annular, sometimes urticarial, erythematous plaque presenting as a manifestation of Lyme disease.*

During the late stages of gout, tophi (urate deposits with surrounding inflammation) occur in the subcutaneous tissues. Improved methods of treatment account for the decrease in the incidence of tophaceous gout in recent years.

Dermatomyositis and psoriatic arthritis are reviewed earlier in this chapter.

Hematologic

Graft-versus-host disease (GVHD) most commonly occurs after bone marrow transplant and represents a constellation of skin lesions, diarrhea, and liver enzyme abnormalities. Acute GVHD begins 7 to 21 days after transplant. The cutaneous abnormalities of acute GVHD include pruritus; numbness or pain of the palms and soles; an erythematous maculopapular eruption of the trunk, palms, and soles; and blisters that, when extensive, resemble toxic epidermal necrolysis. Chronic GVHD begins within months to 1 year after transplant and mainly affects skin and the liver. Early chronic GVHD is characterized by a lichenoid reaction consisting of cutaneous and oral lesions that resemble lichen planus, with coalescing violaceous papules on the skin and white reticulated patches on the buccal mucosa. Late chronic GVHD is characterized by cutaneous sclerosis and scarring alopecia.

Mastocytosis (mast cell disease) can be divided into 4 groups, depending on the age at onset and the presence or absence of systemic involvement: 1) urticaria pigmentosa arising in infancy or adolescence without substantial systemic involvement, 2) urticaria pigmentosa in adults without substantial systemic involvement, 3) systemic mast cell disease, and 4) mast cell leukemia. The cutaneous lesions may be brown-to-red macules, papules, nodules, or plaques that urticate on stroking. Less commonly, the lesions may be bullous, erythrodermic, or telangiectatic. The systemic manifestations are due to histamine release and consist of flushing, tachycardia, and diarrhea.

Necrobiotic xanthogranuloma—indurated plaques with associated atrophy and telangiectasia with or without ulceration—may occur on the trunk or periorbital areas. Serum electrophoresis shows an IgG κ paraproteinemia or multiple myeloma.

Endocrinologic

Diabetes Mellitus

Several dermatologic disorders have been described in diabetes mellitus.

Necrobiosis lipoidica diabeticorum (Figure 26.29) classically occurs on the shins and presents as yellow-brown atrophic telangiectatic plaques that occasionally ulcerate. Two-thirds of patients with this skin disorder have diabetes mellitus (DM).

Granuloma annulare (Figure 26.30) is an asymptomatic eruption consisting of small, firm, flesh-colored or red papules in an annular configuration (less commonly, nodular or generalized). The association with diabetes mellitus is disputed.

Rarely, patients with poorly controlled diabetes mellitus present with spontaneously occurring subepidermal blisters (bullosa diabeticorum) on the dorsal aspects of the hands and feet.

The stiff-hand syndrome has been reported in type 1 DM. Patients have limited joint mobility and tight, waxy skin on the hands. Risk of subsequent renal and retinal microvascular disease is increased.

In scleredema, an insidious onset of thickening and stiffness of the skin occurs on the upper part of the back and posterior aspect of the neck. When scleredema develops, the diabetes mellitus is often long-standing and poorly controlled.

Thyroid

Pretibial myxedema and thyroid acropachy (digital clubbing and swelling) are cutaneous associations of Graves disease.

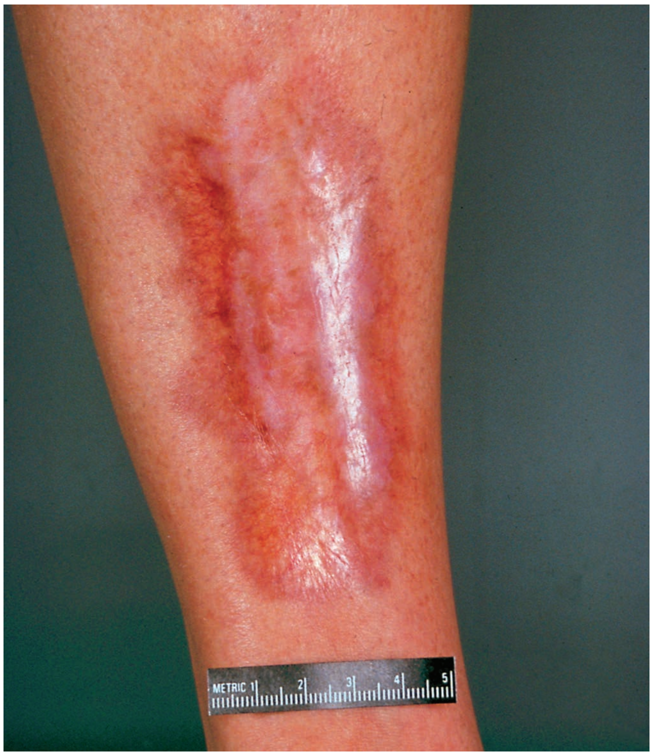


Figure 26.29. *Necrobiosis Lipoidica Diabeticorum.*

KEY FACTS

- ✓ CREST syndrome—*c*alcinosis cutis, *R*aynaud phenomenon, *e*sophageal involvement, *s*clerodactyly, and *t*elangiectasia; associated with circulating anticentromere antibodies
- ✓ Reactive arthritis—triad of urethritis, conjunctivitis, and arthritis, usually in young men; two-third of patients also have skin lesions
- ✓ Graft-versus-host disease—constellation of skin lesions, diarrhea, and liver enzyme abnormalities; most common after bone marrow transplant
- ✓ Mastocytosis can manifest as urticaria pigmentosa without substantial systemic involvement in children or adults
- ✓ Necrobiosis lipoidica diabeticorum—yellow-brown atrophic telangiectatic plaques on shins; two-thirds of patients have DM

Metabolic

The porphyrias are a group of inherited or acquired abnormalities of heme synthesis. Each type is associated with deficient activity of a particular enzyme. The porphyrias are usually divided into 3 types: erythropoietic, hepatic, and mixed.

Erythropoietic porphyria is a hereditary form (autosomal recessive) characterized by marked photosensitivity, blisters, scarring alopecia, hirsutism, red-stained teeth, hemolytic anemia, and splenomegaly. The skin lesions are severely mutilating. Onset is in infancy or early childhood.

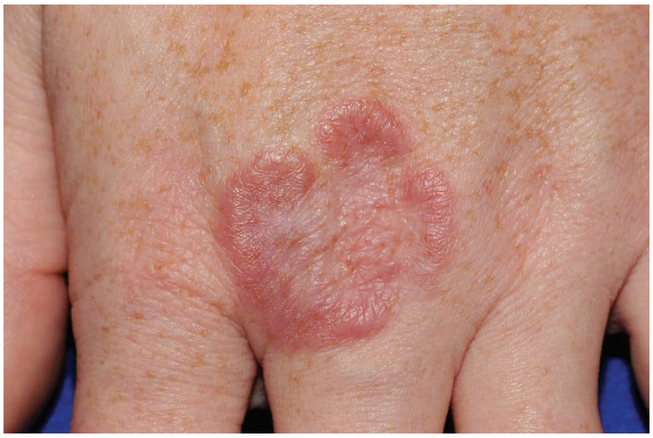


Figure 26.30. *Granuloma Annulare.*

Erythropoietic protoporphyria is an autosomal dominant syndrome that usually begins during childhood. It is characterized by variable degrees of photosensitivity and a marked itching, burning, or stinging sensation that occurs within minutes after sun exposure. Erythropoietic protoporphyria is associated with deficiency of ferrochelatase.

Porphyria cutanea tarda (Figure 26.31), one of the hepatic porphyrias, is the most common form of porphyria. It is an acquired or hereditary (autosomal dominant) disease associated with a defect in uroporphyrinogen decarboxylase. The disease may be precipitated by exposure to toxins (such as chlorinated phenols or hexachlorobenzene), alcohol, estrogens, iron overload, underlying hemochromatosis, and infection with hepatitis C virus. Porphyria cutanea tarda usually presents in the third or fourth decade of life. Clinical manifestations include photosensitivity, skin fragility, erosions and blisters (particularly on dorsal surfaces of the hands), hyperpigmentation, milia, and hypertrichosis. Sclerodermoid skin changes develop in some patients. The diagnosis is confirmed by the finding of increased porphyrin levels in the urine. Treatment includes phlebotomy or low-dose chloroquine.

Acute intermittent porphyria lacks skin lesions. It is characterized by acute attacks of abdominal pain or neurologic symptoms.

Variegate porphyria (mixed porphyria) follows autosomal dominant inheritance. It is characterized by cutaneous abnormalities similar to those of porphyria cutanea tarda and by acute abdominal episodes, as in acute intermittent porphyria. Variegate porphyria tends to be precipitated by the use of drugs, such as barbiturates and sulfonamides.

Nail Clues to Systemic Disease

Onycholysis consists of distal and lateral separation of the nail plate from the nail bed. Onycholysis may be due to psoriasis, lichen planus, infection (such as *Candida* or *Pseudomonas*), a

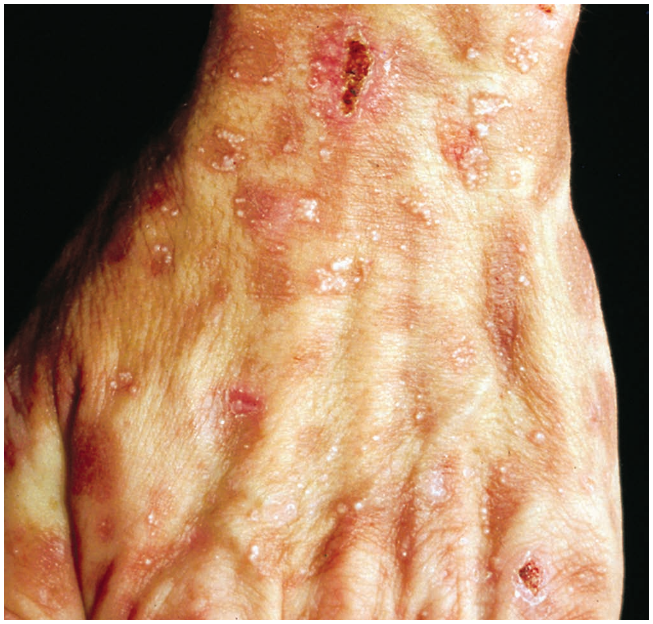


Figure 26.31. *Porphyria Cutanea Tarda.*

reaction to nail cosmetics, or a drug reaction. Drugs noted to induce onycholysis include tetracycline and chlorpromazine. Association with thyroid disease (hyperthyroidism more than hypothyroidism) has also been noted.

Pitting is a common feature of psoriatic nails. Fine, regular nail pitting is associated with alopecia areata.

Terry nails consist of whitening of the proximal or entire nail as a result of changes in the nail bed. This abnormality is associated with cirrhosis.

Muehrcke lines are white parallel bands associated with hypoalbuminemia.

Half-and-half nails (Lindsay nails) are nails in which the proximal half is white and the distal half is red. This abnormality may be associated with renal failure.

Yellow nails are associated with chronic edema, pulmonary disease, pleural effusion, chronic bronchitis, bronchiectasis, and lung carcinoma.

Beau lines are transverse grooves in the nail associated with high fever, chemotherapy, systemic disease, and drugs.

Koilonychia (spoon nails) is associated with iron deficiency anemia, but it also may be idiopathic, familial, or related to trauma.

Blue lunulae are associated with hepatolenticular degeneration (Wilson disease) and argyria.

Mees lines are white bands associated with arsenic exposure.

Cutaneous Manifestations of HIV Infection

Primary infection with HIV results in a flulike illness and an exanthem in 30% to 60% of patients. The exanthem may be morbilliform, vesicular, or similar to pityriasis rosea. Oral ulceration and erosions, genital erosions, and erosive esophagitis also may occur at this stage. The acute exanthem and enanthem are self-limited and often go undiagnosed.

In the early stage of disease, cutaneous manifestations include genital warts, genital herpes, psoriasis, seborrheic dermatitis, xerosis, and pruritic papular eruption. With symptomatic HIV infection (CD4 count, 200-400/mcL), both infections and inflammatory dermatoses occur more frequently. These include psoriasis, seborrheic dermatitis, oral hairy leukoplakia, candidiasis, herpes zoster, adverse drug reactions, herpes simplex, tinea pedis, and onychomycosis.

As the CD4 count decreases to less than 200/mcL, patients may present with a disseminated fungal infection, recurrent or severe herpes zoster, persistent herpes simplex, bacillary angiomatosis, and molluscum contagiosum. Bacillary angiomatosis consists of 1 or more vascular papules or nodules caused by the gram-negative bacteria *Bartonella quintana* and *Bartonella henselae*. Eosinophilic folliculitis, a pruritic eruption primarily involving the head, neck, trunk, and proximal extremities, is characteristic of symptomatic HIV infection. Molluscum contagiosum, a common viral infection of otherwise healthy children, occurs in 10% to 20% of patients with HIV infection.

With advanced HIV infection (CD4 count, <50/mcL), overwhelming infection is characteristic. Infectious agents with skin manifestations include cytomegalovirus, *Cryptococcus*, *Acanthamoeba*, and extensive molluscum contagiosum. Oral hairy leukoplakia is caused by Epstein-Barr virus infection of the oral mucosa and usually occurs among patients with advanced HIV infection.

Epidemic Kaposi sarcoma usually presents as oval papules or plaques oriented along skin lines of the trunk, extremities, face, and mucosa. This presentation is in contrast to that of classic Kaposi sarcoma in elderly patients, which occurs predominantly on the distal lower extremities. Human herpesvirus 8 has been identified in tissue from patients with both epidemic and classic Kaposi sarcoma.

KEY FACTS

- ✓ Porphyria cutanea tarda—most common form of porphyria
- ✓ Pitting of nails—nail characteristic often seen in patients with psoriasis
- ✓ Terry nails—whitening of proximal or entire nail due to changes in nail bed; associated with cirrhosis
- ✓ Primary HIV infection causes flulike illness and an exanthem in 30%-60% of patients
- ✓ Epidemic Kaposi sarcoma—oval papules or plaques along skin lines of trunk, extremities, face, and mucosa

27

Genetics

C. SCOTT COLLINS, MD; CHRISTOPHER M. WITTICH, MD, PharmD

Chromosome Abnormalities

Chromosome abnormalities (Table 27.1) occur in 1 in 180 live births. One-third of these abnormalities are due to autosomal aneuploidy—an abnormal number of chromosomes. Risk factors for autosomal aneuploidy are maternal age 35 years or older and a previous birth of an affected child. The most common **autosomal aneuploidy** syndrome of full-term infants is Down syndrome.

Key Definition

Autosomal aneuploidy: *an abnormal number of chromosomes.*

Single-Gene Defects

Single-gene defects can be due to autosomal dominant, autosomal recessive, and X-linked recessive modes of inheritance. In autosomal dominant inheritance, 1 copy of the gene is sufficient for the trait to be expressed or for the disease to be present (ie, heterozygotes have the disease). There is a 50% chance that any child born to an affected person will inherit the abnormal gene. Penetrance differs among affected persons.

In autosomal recessive inheritance, 1 copy of the abnormal gene is not sufficient to cause disease, and heterozygotes (carriers) are not clinically different from the general population. When 2 persons mate who are heterozygotes for a given gene defect, their children are at 25% risk for inheriting the abnormal gene from both parents and, thus, for having the disease.

X-linked recessive diseases are caused by defects located on the X chromosome. Female heterozygotes who have 1 abnormal gene on 1 X chromosome and 1 normal gene on the other X chromosome usually are clinically normal. Male infants who inherit the abnormal gene have no corresponding genetic loci on the Y chromosome and therefore are referred to as *hemizygotes* and are clinically affected. Any male child born to a heterozygous woman is at 50% risk for having the disease; any female child is at 50% risk for inheriting the gene and being a carrier.

Autosomal Dominant Defects

Table 27.2 lists important autosomal dominant conditions. Other chapters discuss the clinically important autosomal dominant conditions of *BRCA* mutations; hereditary spherocytosis; Huntington disease; low-density lipoprotein receptor deficiency (familial hypercholesterolemia); Lynch syndrome; multiple endocrine neoplasias types I, IIA, and IIB; polycystic kidney disease; and von Willebrand disease.

Key Definition

Osler-Weber-Rendu disease: *hereditary hemorrhagic telangiectasia.*

Autosomal Recessive Defects

Table 27.3 lists important autosomal recessive conditions. The common autosomal recessive conditions discussed in other chapters are α_1-antitrypsin deficiency, cystic fibrosis,

Table 27.1 • Genetic Disorders Caused by Chromosome Abnormalities

Syndrome/Genetic Abnormality	Features
Down/Trisomy 21	Risk present when maternal age ≥35 y Congenital heart defects (VSD and AV canal defects) Early-onset Alzheimer dementia Mild to moderate intellectual disability Median survival of 60 y Increased risk of acute lymphocytic leukemia
Klinefelter/47,XXY	Tall, eunuchoid habitus Small testes Infertility Increased risk of germ cell tumors
Turner/45,X	Mentally normal Short stature, webbed neck Lack of secondary sex characteristics 30% risk of bicuspid aortic valve or aortic coarctation Increased risk of ascending aortic aneurysm Possibly Y chromosome material (eg, 45,X/46,XY mosaicism) and increased risk of gonadal cancer
Fragile X-linked/ Trinucleotide repeat (CGG) expansions on X chromosome	May be physically normal or have a long thin face, prominent jaw, large ears, and enlarged testes Mild to profound intellectual disability

Abbreviations: AV, atrioventricular; VSD, ventricular septal defect.

Table 27.2 • Selected Autosomal Dominant Genetic Disorders

Disorder/Genetic Abnormality	Features
Classical Ehlers-Danlos syndrome/ Defect in gene coding for collagen[a]	Velvety textured, hyperextensible, and fragile skin Joints are hyperextensible and prone to dislocation Mitral valve prolapse occurs in many patients Most severe form results in tendency for arterial aneurysms and visceral organ rupture
Marfan syndrome/ Defect in fibrillin-1 gene	Involves musculoskeletal, ocular, and cardiovascular systems Tall stature, scoliosis or kyphosis, and pectus deformities Dislocations of the lens occur in 50%-80% of patients; all patients should have ophthalmologic evaluation Cardiovascular manifestations include mitral valve prolapse and dilatation of the ascending aorta β-Adrenergic blockers might delay progressive aortic dilatation Surgical treatment is often successful for mitral and aortic regurgitation and aortic dissection About 20% of cases arise through new mutation
Myotonic dystrophy/ Triplet repeat expansion in myotonin protein kinase gene	Most common form of muscular dystrophy in adults Diagnosis based on clinical findings and typical electromyographic pattern characterized by prolonged rhythmic discharges Genetic counseling warranted for patients and family members Onset usually in second to third decade of life Myotonia, muscle atrophy and weakness, ptosis of eyelids, expressionless facies, and premature frontal baldness Testicular atrophy or menstrual irregularities, gastrointestinal tract symptoms Diabetes mellitus occurs in 6% of patients Cardiac disease occurs in two-thirds of patients, and sudden death may occur Sleep-related central and respiratory muscle hypoventilation are common
Neurofibromatosis 1 and 2/ Multiple different mutations identified	Neurofibromatosis 1 has markedly variable expression but high penetrance Malignancy (often peripheral nerve sheath tumors) in approximately 10% of patients Characteristics of neurofibromatosis 2 are vestibular schwannomas, nervous system gliomas, and subcapsular cataracts
Osler-Weber-Rendu disease (hereditary hemorrhagic telangiectasia)/ Multiple genetic defects identified	Characterized by abnormal blood vessel formation in skin, mucous membranes, lungs, liver, and brain Arteriovenous malformations occur in larger organs Nosebleeds and gastrointestinal tract bleeding are common

Table 27.2 • Continued

Disorder/Genetic Abnormality	Features
Tuberous sclerosis complex/ One gene defect located on chromosome 9 (hamartin), another on chromosome 16 (tuberin)	About 50% of cases arise from new mutation Characterized by nodules of brain and retina, seizures, mental retardation in <50% of cases, depigmented "ash leaf" or "confetti" macules, facial angiofibromas, dental pits, subungual fibromas, and angiomyolipomas
Von Hippel-Lindau disease/ *VHL* localized to chromosome 3p25-26[b]	Typical case: retinal, spinal cord, and cerebellar hemangioblastomas; cysts of kidneys, pancreas, and epididymis Renal cysts, hemangiomas, and benign adenomas are usually asymptomatic Retinal hemangioblastomas may be earliest manifestation Periodic magnetic resonance imaging with gadolinium is recommended Renal cancer is major cause of death

[a] Defect varies by syndrome subtype.

[b] The normal gene has a central role in cellular response to hypoxia and acts as a tumor suppressor.

hemochromatosis, sickle cell anemia, the thalassemias, and Wilson disease.

X-Linked Recessive Defects

Table 27.4 lists a clinically important X-linked recessive condition. Two other important X-linked recessive diseases, hemophilia A and B, are discussed in other chapters.

Mitochondrial Mutations

Mitochondrial disorders can arise as new mutations or can be maternally inherited. Many mitochondrial enzymes, including most of the respiratory chain complex, are encoded by nuclear DNA and transported into the mitochondria. Mitochondrial DNA mutations cause Leber optic atrophy and the multisystem syndromes MELAS (mitochondrial myopathy, encephalopathy, episodes of lactic acidosis, and stroke), MERRF (myoclonic epilepsy with ragged red fibers), and NARP (neuropathy, ataxia, and retinitis pigmentosa).

Table 27.3 • Selected Autosomal Recessive Genetic Disorders

Disorder/Genetic Abnormality	Features
Friedreich ataxia/ *FXN*, localized to chromosome 9q13[a]	Ataxic gait is first sign of the disease Mean age at onset, approximately 12 y Dysarthria, hypotonic muscle weakness, loss of vibration and position senses, and loss of deep tendon reflexes subsequently Cardiomyopathy is major cause of death
Gaucher disease/ Deficiency of enzyme glucocerebrosidase; results in lipid storage in spleen, liver, bone marrow, and other organs	Frequent in Ashkenazi Jews May be asymptomatic or present in childhood or adulthood with hepatosplenomegaly, thrombocytopenia, anemia, degenerative bone disease, osteoporosis, or pulmonary disease Enzyme replacement and substrate reduction therapies are effective for nonneuronopathic Gaucher disease

[a] The most frequent mechanism of mutation is expansion of a GAA trinucleotide repeat that results in abnormal accumulation of intramitochondrial iron.

Table 27.4 • A Selected X-Linked Recessive Genetic Disorder

Disorder/Genetic Abnormality	Features
G6PD enzyme deficiency/ Abnormally low G6PD levels	G6PD is important in red blood cell metabolism Most common human enzyme defect May involve hemolytic anemia due to infection, fava ingestion, or use of medications, including antimalarials (primaquine and chloroquine), sulfa drugs, and isoniazid Heinz bodies on peripheral smear Negative Coombs test

Abbreviation: G6PD, glucose-6-phosphate dehydrogenase.

KEY FACTS

✓ Down syndrome—the most common autosomal aneuploidy syndrome in full-term infants

✓ Autosomal dominant, autosomal recessive, and X-linked recessive—3 modes of inheritance of single-gene defect

✓ Genetic disorders caused by chromosome abnormalities include Down, Klinefelter, Turner, and fragile X-linked syndromes

✓ Peripheral nerve sheath tumors can occur in neurofibromatosis 1; vestibular schwannomas, nervous system gliomas, and subcapsular cataracts that characterize neurofibromatosis 2

28

Geriatrics

ERICKA E. TUNG, MD

Geriatric Assessment

The overarching goal of the geriatric assessment is to develop a holistic understanding of the older patient as a means to identify emerging problems and individual capabilities. This information guides treatment, care coordination, and evaluation of long-term care needs. Assessment of the older adult requires a multifaceted approach that encompasses physical, cognitive, and psychosocial domains. The comprehensive geriatric assessment takes this approach a step further. It is *targeted* toward the frail older adult and involves an interdisciplinary team of geriatric care providers. Both the general assessment and the comprehensive assessment aim to enhance quality of life and optimize function. Given the time constraints placed on practicing physicians, a strategy of rapid screening of key geriatric domains, followed by a more in-depth assessment of worrisome areas, is an effective approach. The subsequent sections of this chapter describe the central components of the geriatric assessment.

Functional Status

The capacity of persons to do tasks required of them by their environment carries importance in the geriatric assessment. Functional status decline may be the harbinger of a previously undiagnosed medical condition or a manifestation of mismatch between an individual's needs and social support structure. Further, indicators of functional status are strong predictors of death, (re)hospitalization, and institutionalization. Of note, an older person's functional state is dynamic; for example, illness or prolonged hospitalization may cause a dramatic decline in functional status.

Most validated functional status tools evaluate 3 tiers of activity: basic activities of daily living (ADLs), the simplest activities required to remain independent; instrumental ADLs, the more complex activities required to maintain a household; and advanced ADLs, the activities required to thrive and interact within one's own community. Examples of the tasks in each tier are listed in Table 28.1.

Performance-based testing of mobility and function can be achieved by observing gait, balance, and transfers (Box 28.1). Among the diverse functional performance indicators, gait speed is recognized as a strong predictor of future disability and death and has been termed the *sixth vital sign* for older adults. A clinician can measure gait speed by timing a patient as the patient walks a 4-m route (first as quickly as the patient can and then at a usual pace). A gait speed of 0.8 m/sec allows for independent community ambulation. Patients with speeds faster than 1.0 m/sec typically have healthier aging and life expectancy beyond the mean for their age and sex. Finally, the clinician must integrate knowledge about the older patient's living environment, goals of care, and current support structure with the results of the functional status assessment to determine whether additional support services are needed.

Falls

Between 30% and 40% of community-dwelling older adults fall each year, and 1 in 10 falls results in serious injury such as fracture or traumatic brain injury. In addition, falls may lead to prolonged functional decline and death. The increased frequency of falls among elderly persons reflects a complex intersection between predisposing or intrinsic factors and precipitating or extrinsic risk factors. Predisposing factors can be normal age-related changes (eg, reduced depth perception, contrast sensitivity, lower extremity proprioceptive capacity) and disease-related changes (eg, dementia-related impulsivity, peripheral neuropathy due to diabetes mellitus). Precipitating factors include inappropriate choice of gait aid, environmental hazards, and risk-taking behaviors. Prevention of falls requires

Table 28.1 • Functional Status Assessment

Functional Status Tier	Tasks
Basic/self-care	Bathing Dressing Toileting/maintenance of continence Transferring from bed to chair Grooming Feeding oneself
Instrumental	Managing finances Taking medications Use of telephone Use of transportation Housework/laundry Meal preparation Shopping
Advanced	Participation at faith organization Volunteerism

the clinician to consider an individual's specific risk factors for this common geriatric problem. Examples of independent risk factors for falls include a history of previous falls, balance impairment, muscle weakness, psychoactive medication use, and gait instability.

Screening for Falls

A recently updated guideline from the American Geriatrics Society and the British Geriatrics Society (AGS/BGS) suggests that all persons aged 65 years or older should be screened annually for falls. This guideline suggests that persons who have fallen 2 or more times in the past year, present with fall-related injury, or report or display an unsteady gait should undergo assessment of their risk factors and corresponding risk factor mitigation.

Evaluation of Falls

Patients who are at high risk for falls on the basis of the AGS/BGS risk stratification method should undergo a multidimensional assessment. The patient should be asked specifically about the circumstances surrounding the fall, prodromal symptoms, and loss of consciousness. A loss of consciousness may suggest an acute cardiac or neurologic event. The high-risk patient should be assessed for known risk factors. The use of prescription and over-the-counter medications should be assessed. Psychotropic medications, including antidepressants, antipsychotics, and benzodiazepines, have been associated with increased risk of falls and hip fracture.

Box 28.1 • Tests to Assess Gait, Balance, and Strength

Timed Up and Go Test
30-Second Chair Stand Test
Functional Reach Test
4-Stage Balance Test
Berg Balance Scale

The physical examination for a person at risk for falls should begin with measurement of orthostatic vital signs. As people age, baroreflex sensitivity declines, manifested as a decreased ability to increase heart rate in response to positional change. In addition, total body water declines with advancing age. Both physiologic changes can lead to orthostasis. The physical examination should include targeted cardiovascular, neurologic, and ophthalmologic examinations. A valid assessment of gait, balance, and strength is a necessary part of the physical examination. Frequently used tests are listed in Box 28.1.

Additional testing such as laboratory tests or Holter monitoring should be performed only when driven by the findings of the history and physical examination.

Treatment and Prevention of Future Falls

Evidence-based interventions for the treatment and prevention of future falls have been reviewed critically and incorporated into guidelines from the US Preventive Services Task Force and the AGS/BGS. Choice of targeted interventions is based on the findings of the assessment (Box 28.2).

KEY FACTS

✓ Geriatric assessment requires a multifaceted—physical, cognitive, and psychosocial—approach

✓ Gait speed—a strong predictor of future disability and death in older adults

✓ Precipitating factors in falls—a wrong choice of gait aid, environmental hazards, risk-taking behaviors

✓ Psychotropic medications may increase the risk of falls and hip fracture

✓ Exercise therapy (focusing on strength and balance) and vitamin D supplementation are effective fall prevention interventions

Cognitive Impairment

Mild Cognitive Impairment

A broad spectrum of neurocognitive changes occur commonly with aging, ranging from the occasional memory lapses that are common for people of all ages to overt dementia. Mild cognitive impairment (MCI) represents a heterogeneous intermediate stage between normal aging and dementia. The prevalence

Box 28.2 • Treatment and Prevention of Falls for Community-Dwelling Older Adults

- Exercise and physical therapy program focused on balance and strength (eg, tai chi)
- Vitamin D supplementation
- Treatment of vision impairment
- Management of postural hypotension
- Pacemaker placement in patients with carotid sinus hypersensitivity
- Psychoactive medication use reduction or elimination
- Multifactorial interventions based on mitigation of a person's fall-related risk factors. Such interventions can reduce falls for those at very high risk

of MCI in population-based studies of adults aged 70 years and older ranges from 14% to 18%. These persons are at increased risk for progression to dementia (with an approximately 10% risk of progression per year), making it important for clinicians to recognize MCI and provide appropriate anticipatory guidance to patients and their loved ones.

MCI can manifest as 1 of 2 major subtypes: amnestic MCI or nonamnestic MCI. The former is more likely to progress to Alzheimer disease (AD), whereas the latter may progress to non-AD dementia subtypes. Persons with MCI show noticeable changes in cognition that are not yet severe enough to negatively affect functional capacity. To date, no medications have been shown to decrease the rate of conversion to dementia. Randomized controlled trials examining the effect of exercise and cognitive rehabilitation for patients with MCI have shown small improvements in cognitive function.

Dementia

The general term *dementia*, also now called *major neurocognitive disorder*, encompasses several disorders or subtypes of cognitive impairment that are progressive, are nonreversible, and have noticeable impact on the affected individual's function. These disturbances are not accounted for by another mental disorder or delirium. Dementia is a disease of later life; in the United States, at least 8% of persons older than 65 years and 35% to 50% older than 85 years have this geriatric syndrome. Cognitive domains that can be affected include learning and memory, language, executive function, complex attention, perceptual-motor function, and social cognition.

Although the evidence is insufficient for universal screening, clinicians must investigate when older patients present with memory concerns, nonadherence, functional decline, or new psychiatric symptoms. Clinicians must use collateral history from a reliable informant, patient-provided history, and a standardized mental status examination when evaluating such symptoms. In the differential diagnosis of cognitive difficulties, clinicians need to consider the reversible conditions such as depression, long-term alcohol abuse, medications, metabolic disorders, toxic agents, nutritional deficiencies, normal-pressure hydrocephalus, subdural hematoma, and central nervous system tumors and infections. Recommended laboratory and imaging studies are listed in Box 28.3.

Box 28.3 • Workup of Dementia

- Laboratory tests
  - All patients:
    - Thyrotropin (TSH)
    - Vitamin B_{12} level
  - Based on clinical suspicion:
    - Complete blood cell count
    - Electrolytes
    - Glucose
    - Renal and liver function tests
    - Testing for neurosyphilis, HIV infection
    - Erythrocyte sedimentation rate
- Neuroimaging
  - Most useful in younger patients and patients with rapid progression, focal neurologic deficits, symptoms of normal-pressure hydrocephalus, recent head trauma
  - Noncontrast-medium head computed tomography
  - Magnetic resonance imaging

Abbreviation: TSH, thyroid-stimulating hormone.

The major subtypes and classic clinical features of dementia are listed in Table 28.2.

Treatment of Cognitive Impairment

Dementia

Nonpharmacologic treatment is paramount for all patients who have neurocognitive impairment. Important nonpharmacologic considerations are listed in Box 28.4.

Several factors must be considered before starting a medication for a patient with dementia. They include renal clearance, potential for drug interactions, potential for adverse drug effects, and the patient's goals of care. Medications with anticholinergic activity can worsen cognitive function in patients with dementia.

Cognitive Enhancement Medications

Acetylcholinesterase inhibitors (ie, donepezil, rivastigmine, tacrine, and galantamine) are approved by the US Food and Drug Administration (FDA) for the treatment of AD. Although acetylcholinesterase inhibitors are not considered disease-modifying drugs, they may delay symptom progression transiently. Improvement in abnormal behaviors associated with dementia also may occur with their use. Studies have shown

Table 28.2 • Major Subtypes of Dementia: Major Neurocognitive Disorder Subtypes

Subtype	Clinical Features	Imaging	Other
Alzheimer disease	Early deficits: • Selective memory impairment • Executive dysfunction • Visuospatial impairment Neuropsychiatric symptoms become more common in middle-late course of disease	• Generalized and focal atrophy • Hippocampal atrophy • Medial temporal lobe atrophy	• Most common cause of dementia • Life expectancy after diagnosis is 3-11 years
Dementia with Lewy bodies (DLB)	Distinctive features: • Visual hallucinations • Parkinsonism • Fluctuations in cognition • Dysautonomia • REM sleep behavior disorder	• Generalized atrophy • Reduced dopamine transporter uptake in basal ganglia by SPECT or PET	• 30%-50% have severe sensitivity to antipsychotic medications • Recurrent falls are common • Dementia occurs before or shortly after parkinsonism
Parkinson disease dementia (PDD)	• Executive dysfunction • Visuospatial dysfunction • Preserved language function • Paranoid delusions • Overlap with DLB	• Generalized atrophy	• Pathologic hallmark: Lewy bodies • Dementia occurs in setting of long-standing Parkinson disease (PD) • Prevalence increases with duration of PD
Vascular dementia	Cortical syndrome • Cognitive features specific to areas affected • Ex. left parietal: aphasia, apraxia, agnosia Subcortical syndrome • Chronic ischemia and lacunar infarcts affect deeper structures • Ex. focal motor symptoms, early gait disturbance	• Cortical or subcortical infarctions • Ischemic changes • Cerebral white matter lesions are common but nonspecific	• Vascular risk factors must be managed • Life expectancy after diagnosis is 3-5 years
Frontotemporal dementia (FTD)	Behavioral variant FTD • Most common subtype • Progressive change in personality and behavior • Disinhibition, lack of empathy Primary progressive aphasia • Gradual language impairment • Preserved memory	• Early imaging may be normal • Focal frontal or temporal atrophy	• Disease onset usually occurs in the sixth decade

Abbreviations: ex, example; PET, positron emission tomography; REM, rapid eye movement; SPECT, single-photon emission computed tomography.

modest benefit for acetylcholinesterase inhibitors in dementia with Lewy bodies and Parkinson disease dementia. The high prevalence of liver toxicity associated with tacrine has not been found with the other acetylcholinesterase inhibitors. Common adverse effects include nausea, vomiting, bradycardia, diarrhea, and anorexia.

Memantine, an *N*-methyl-D-aspartate antagonist, is FDA approved for the treatment of moderate to severe AD. This medication is postulated to have neuroprotective effects through its reduction of glutamate-mediated excitotoxicity. Its most common adverse effects are dizziness, headache, and constipation. Increased confusion and hallucinations have been reported. This

Box 28.4 • Nonpharmacologic Treatment of Dementia

Cognitive rehabilitation

Supportive therapy

Physical exercise

Caregiver education and support

Environmental modification (eg, controlled amount of stimulation, routine schedule)

Safety enhancement (eg, fall prevention, driving assessment)

Anticipatory guidance and advance care planning medication can be used as a single agent or in conjunction with an acetylcholinesterase inhibitor. However, the DOMINO-AD (Donepezil and Memantine in Moderate to Severe Alzheimer's Disease) trial found that the addition of memantine to donepezil in moderate or severe AD was no more effective than donepezil alone. Evidence for cognitive enhancement medications in vascular dementia has been inconclusive.

Over-the-counter supplements such as *Ginkgo biloba* and nonsteroidal anti-inflammatory drugs are not supported by sufficient data to recommend their use in dementia. Data on the use of vitamin E have been mixed; however, this supplement may result in slower functional decline for patients with mild to moderate AD.

Behavioral Dyscontrol

The neuropsychiatric symptoms associated with all subtypes of dementia are often more troublesome to patients and caregivers than the cognitive symptoms inherent to these conditions. Nonpharmacologic interventions are recommended as the first step for neuropsychiatric symptoms. These interventions should be individualized and should capitalize on the patient's preserved procedural memory. Pharmacologic therapy brings with it considerable risk of adverse drug events and should be used only if the patient's distressing symptoms are refractory to nonpharmacologic interventions or create a dangerous situation. In this population, antipsychotic agents are associated with increased risk of death, stroke, falls, and infections.

Delirium

Delirium is an acute confusional state marked by inattention, fluctuating course, and abnormal level of consciousness. It is the prototypical geriatric syndrome and represents the final common pathway of the intersection between predisposing characteristics and precipitating factors (Figure 28.1). Delirium is one of the most common complications after a surgical procedure for older adults and may affect one-half of older adults undergoing hip fracture operation and coronary artery bypass grafting. Baseline neurocognitive disorders are an important risk factor for delirium.

Key Definition

Delirium: *acute confusional state marked by inattention, fluctuating course, and abnormal level of consciousness.*

Delirium is a medical emergency, and clinicians must be attuned to its detection. Key diagnostic features are listed in Box 28.5. Delirium is diagnosed with a brief cognitive screening test and a validated delirium instrument such as the Confusion Assessment Method. Laboratory evaluation can help to identify correctable precipitating factors. Choice of laboratory and imaging studies should be driven by clinical suspicion and may include a complete blood cell count, complete metabolic profile, liver enzyme tests, urinalysis, chest radiograph, electrocardiography, and drug or toxin levels. Brain imaging, cerebrospinal fluid evaluation, and electroencephalography are needed only when there is a strong clinical suspicion of a primary neurologic cause. All medications should be reviewed, with particular attention to psychoactive medications.

Prevention is always the best strategy. Multicomponent efforts aimed at targeting risk factors, such as sleep disruption, immobility, sensory impairment, dehydration, and cognitive impairment, have been successful in reducing the incidence of delirium. Treatment is largely supportive and begins with mitigation of contributing factors. Examples include environmental simplification, optimization of sensory input, and regulation of sleep-wake cycle. Delirious patients are at risk for iatrogenic complications, so careful surveillance and preventive strategies are important. No FDA-approved medications are available to treat delirium, and pharmacologic therapies should be used cautiously because they may actually prolong the syndrome. Medications may be necessary to control frightening psychotic symptoms or dangerous behaviors.

Late-Life Depression

Late-life depression is especially common among persons receiving long-term care and those with multiple comorbidities. Older adults with depression are more likely than their younger counterparts to present with somatic symptoms such as pain or unexplained weight loss. This condition can be challenging to diagnose because comorbid conditions and their associated treatments often result in overlap symptoms such as fatigue, memory impairment, and sleep disturbance. Screening for the presence of low mood and anhedonia is a recommended initial strategy because these 2 symptoms are less likely to be confounded by medical illnesses. The Patient Health Questionnaire 9 can be used for screening and for assessment of treatment response. The Geriatric Depression Scale is often used in this population because it offers yes-no responses and does not include somatic and sleep-related questions. It is useful for screening and diagnosis but not for measurement of response to treatment.

Although older patients attempt suicide less often than younger patients, they are more likely to complete the suicide attempt. White men aged 85 years and older have the highest risk of completed suicide. Clinicians should screen older patients for suicidality and intervene, when necessary, with collaborative care interventions.

Undernutrition

Normal aging results in predictable changes in body composition, including increased fat mass and decreases in bone mass,

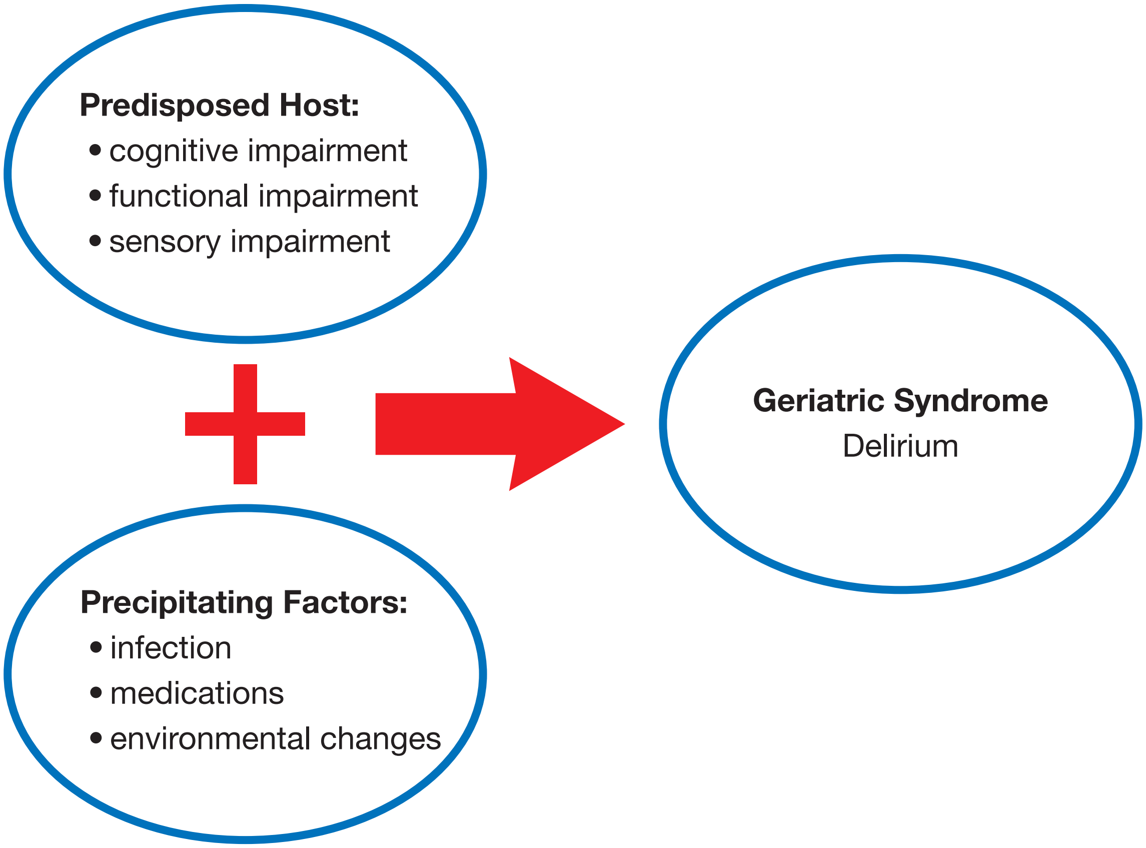


Figure 28.1. *Delirium as a Geriatric Syndrome.*

lean muscle mass, and water content. Normal aging is also associated with reduced ability to concentrate urine, reduced thirst perception, and impaired response to serum osmolarity, culminating in increased risk of dehydration.

Both undernutrition and obesity are common among older US adults and increase the risk of morbidity, functional decline, and death. Unintended weight loss may reflect inadequate dietary intake, anorexia, sarcopenia, or the inflammatory effects of an underlying illness. Screening tools such as the Malnutrition Universal Screening Tool or Mini Nutritional Assessment can identify malnourished older adults or those at risk for malnutrition. Other than body mass index, anthropometric tools are often impractical for use in the ambulatory primary care setting. Laboratory markers that reflect undernutrition and have been correlated with increased death among the elderly population include hypoalbuminemia and low serum levels of cholesterol. However, serum albumin is also affected by other factors such as inflammation, thereby limiting its use as a screening tool.

Box 28.5 • Key Diagnostic Features of Delirium

Acute change[a] in mental status and fluctuating course

Difficulty focusing attention

Disorganized or incoherent thinking

Abnormal level of consciousness (eg, hyperalert, lethargic, stuporous, comatose)

[a] Changes typically occur over hours to days.

Advance Care Planning

Advance care planning is a process for persons to communicate their preferences for medical care, should they ever lose the capacity to make medical decisions or articulate their wishes. Completion of an advance health care directive is an important element of this process and should be strongly encouraged.

The 2 most common types of advance medical directives are durable power of attorney for health care, which designates a proxy decision maker for health-related decisions, and an instructional directive or living will, which allows an individual to communicate his or her preferences for specific types of medical care in future states of health.

KEY FACTS

- ✓ If parkinsonian symptoms present at the same time as cognitive symptoms or shortly afterward, dementia with Lewy bodies is more likely than Parkinson disease dementia
- ✓ Acetylcholinesterase inhibitors do not change the course of AD but may slow its symptoms
- ✓ Confusion Assessment Method—a helpful screening tool to supplement the history and physical examination of patients with acute mental status changes
- ✓ Pharmacologic therapies may actually prolong delirium and need to be used with caution
- ✓ Advance directive documents—activated only if the patient loses decision-making capacity

Vision Loss

Vision impairment is defined as visual acuity of 20/40 or worse; **blindness** is defined as visual acuity of 20/200 or worse. Both increase with advancing age; more than 25% of people older than 85 years have serious visual impairment. The American Academy of Ophthalmology recommends a comprehensive eye examination every 1 to 2 years for older adults. However, the US Preventive Services Task Force has concluded that the evidence is insufficient to recommend for or against routine vision screening among asymptomatic older adults. New eye symptoms in an older adult should be thoroughly evaluated because vision impairment is associated with decreased quality of life, falls, and motor vehicle crashes in this population.

Key Definitions

Vision impairment: *visual acuity of 20/40 or worse.*
Blindness: *visual acuity of 20/200 or worse.*

Worldwide, the 2 leading causes of visual impairment are refractive error and cataracts. The most common refractive error in older adults is increasing hyperopia (farsightedness) with age. Cataract extraction has consistently been a well-tolerated operation in the older population and has shown improvements in important outcomes such as vision-related quality of life and fall rate.

Age-related macular degeneration (AMD) is a leading cause of irreversible blindness in elderly persons and has 2 main types. The dry form is usually of slower onset, whereas the wet form can result in more sudden central vision loss. Risk factors for AMD include advancing age, family history of AMD, and cardiovascular risk factors, such as hypertension and cigarette smoking. Chapter 32, "Otolaryngology and Ophthalmology," has further information about AMD risk factors.

Glaucoma is the second leading cause of irreversible blindness worldwide and the most common cause of blindness in African Americans. Increased intraocular pressure is an important risk factor for the optic nerve damage and visual field loss most commonly associated with this syndrome. Primary open-angle glaucoma characterized by blocked passage of aqueous humor is much more common and indolent than acute angle-closure glaucoma, which happens more suddenly and presents with a painful red eye and acute vision loss. Both are described in Chapter 32, "Otolaryngology and Ophthalmology."

Hearing Loss

Hearing loss is a common, underrecognized condition among older adults that profoundly affects quality of life. It is typically multifactorial in older patients and may present atypically with social withdrawal or low mood. Evaluation of hearing loss should include a careful physical examination of the ear to evaluate for structural abnormality (eg, cerumen impaction, otitis), as well as a valid screening test. Options for testing include self-assessment questionnaires, office-based examination techniques (eg, whispered voice test), and handheld tone-emitting otoscopes. If an abnormality is identified with 1 of these 3 tests, the Weber and Rinne tests can help the clinician elucidate the anatomical cause of the hearing loss (Table 28.3). When objective hearing loss is identified, patients should be offered referral

Table 28.3 • Differentiating Sensorineural vs Conductive Hearing Loss

	Hearing Loss	
Factor	**Sensorineural**	**Conductive**
Anatomy	Cochlear/retrocochlear	External ear/middle ear
Sample causes	Drug-induced hearing loss Labyrinthitis	Cerumen impaction Cholesteatoma Otitis media
Weber test[a]	Lateralizes to better-hearing ear	Louder in affected ear
Rinne test[b]	Both bone and air conduction are equally suppressed	Air-conducted sound is not heard

[a] For Weber test, the clinician strikes the tuning fork and places it gently against a midline structure of the skull (midforehead or vertex). Normally, sound should be transmitted to both sides equally.

[b] For Rinne test, the clinician strikes the tuning fork and places it on the mastoid bone. When the patient ceases to hear the vibration, the clinician moves the tines close to the external auditory meatus to check air conduction. Normally, sound should persist through air conduction for an additional 30 to 60 seconds.

for a formal audiologic evaluation. If the hearing loss occurs suddenly, oral corticosteroid therapy and urgent otolaryngologic referral should be considered.

Numerous hearing aid options exist. Providers must also counsel hearing-impaired patients about the utility of adaptive equipment and future avoidance of ototoxic medications (eg, aminoglycosides, cisplatin, vancomycin, loop diuretics, salicylates).

Surgical management is often required for mechanical problems that have led to conductive loss. Cochlear implants can be very effective for older adults with severe, bilateral, sensorineural hearing loss that has been refractory to hearing aids. Cochlear implants function by bypassing the damaged cochlear hair cells and providing direct electrical stimulation to the auditory nerve fibers of the cochlea. These signals are then sent to the auditory system of the brain. Patients must be motivated, fit for general anesthesia, and capable of participation in postimplant rehabilitation.

Pressure Ulcers

Pressure ulcers are most common among older adults who are hospitalized or receiving long-term care services. They cause serious morbidity among frail older adults. Compression of the skin overlying bony prominences such as the sacrum, greater trochanter, and calcaneus is most common, but pressure ulcers also can result from poorly fitting appliances such as splints and casts. Prevention of pressure ulcers is of paramount importance and begins with the identification of patients at risk. Preventive strategies for pressure ulcers are listed in Box 28.6.

Pressure ulcers can be classified on the basis of the National Pressure Ulcer Advisory Panel staging system as follows.

Stage I: Nonblanchable erythema of intact skin. There may be associated edema.

Stage II: Partial-thickness skin loss with exposed dermis. The ulcer is superficial and may present as a blister or shallow crater with a red wound bed.

Box 28.6 • Preventive Strategies for Pressure Ulcers

Frequently reposition bed-bound patients. A 2-hour minimum interval between assisted turnings is recommended

Do not elevate the head of the bed more than 30°, to prevent friction-induced injury

Choose the appropriate support surface on the basis of patient characteristics

Minimize exposure to excessive moisture

Ensure optimal protein intake

Avoid excessive dryness and scaling with the use of lotions that contain fatty acids

Box 28.7 • General Treatment Strategies for Pressure Ulcers

Relieve pressure over the ulcer with appropriate positioning and support surfaces

Débride nonviable tissue

Optimize the wound environment (prevent wound maceration and avoid friction and shearing forces) to promote the formation of granulation tissue[a]

Manage other conditions (malnutrition or infection when present) that may delay wound healing

Manage pain

[a] Specific treatment (wound dressing and coverage) is dependent on pressure ulcer stage.

Stage III: Full-thickness tissue loss with damage or necrosis of subcutaneous tissue. The damage may extend to the fascia. The ulcer is a deep crater.

Stage IV: Full-thickness skin loss with exposed muscle, bone, or tendons. Sinus tracts may be present.

Unstageable/unclassified: Full-thickness skin or tissue loss—depth unknown. Full-thickness tissue loss occurs in which the actual depth of the ulcer is obscured by slough (yellowish tan exudate) or eschar (brown or black). Typically, these are stage III or IV. Stable (ie, no sign of infection) eschar on the heels should not be removed.

Suspected deep tissue injury: The intact skin over a bony prominence appears purple or maroon. A blood-filled blister may be associated. Deep tissue injury may progress rapidly despite optimal treatment.

Treatment of pressure ulcers depends on the depth and extent of the wound (Box 28.7).

Urinary Incontinence

Urinary incontinence is common among older adults and increases the risk of urinary tract infection (UTI), skin breakdown, social isolation, and depression. Urinary incontinence affects caregiver burden and continues to be an important reason for nursing home placement.

Evaluation of Incontinence

The evaluation of urinary incontinence includes a thorough medical history, physical examination, and several selected laboratory tests. The history should include urine volume, duration of symptoms, precipitating factors, functional status, and assessment of whether symptoms of obstruction exist (low urinary force of stream, sensation of incomplete bladder emptying, and hesitancy). In addition, symptoms of neurologic disease, associated disease states, menstrual status and parity, and medications should be documented. Medications that may worsen incontinence include diuretics, cholinesterase inhibitors, calcium channel antagonists, narcotic analgesics, sedative-hypnotics, and oral estrogen. Red flag symptoms, such as sudden development of incontinence, pelvic pain, or hematuria, require prompt workup.

Physical examination of the abdomen should evaluate bladder distention and possible abdominal masses. Examination of the pelvis should include a pelvic examination, rectal examination, and neurologic evaluation (with testing of sacral cord function).

The workup for incontinence should always include a urinalysis, a voiding diary, and a postvoid residual volume measurement. Urodynamic studies are occasionally indicated to establish the diagnosis of incontinence when the patient has a medically confusing history or more than 1 type of urinary incontinence (so-called mixed incontinence).

Types of Incontinence

Several mechanisms contribute to urinary incontinence. They can be categorized as *urge incontinence, stress incontinence, mixed urge-stress incontinence*, and *overflow incontinence*. Patients are said to have *functional incontinence* if they have a condition such as cognitive impairment or difficulty with ambulation that limits their ability to reach the toilet. Features of each type and treatment options are described in Table 28.4.

Urinary Tract Infections

UTIs are one of the most common bacterial infections of older adults. Functional impairment, incomplete emptying of the bladder, urinary instrumentation, and catheterization all predispose elderly persons to UTI. Among community-dwelling women, the most common pathogens in UTIs are *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis*, and *Enterococcus faecalis*. Rates of antibiotic resistance are on the increase among these pathogens, including fluoroquinolone-resistant *E coli*.

Asymptomatic bacteriuria becomes more common with age, and 6% to 16% of women in the community and 25% to 54% of women in nursing homes are affected. Asymptomatic bacteriuria is a colonization state and should not be treated because treatment can lead to selection of resistant organisms and the potential for adverse drug events.

Only symptomatic patients should be evaluated with urinalysis and urine culture. Symptoms specific for UTI, such as acute dysuria, new or worsening urgency, increase in frequency, new incontinence, suprapubic or costovertebral pain, or fever, should prompt the clinician to consider urine studies. Repeated urine testing to assess for cure is not indicated. Chapter 49, “Sexually Transmitted, Urinary Tract, and Gastrointestinal Tract Infections,” provides information on treatment of UTI.

Sexual Function and Sexuality

Multiple physical and psychosocial changes that occur with aging can affect sexuality in later life. In men, erections may be less reliable and durable and may require more direct stimulation. Refractory periods are more prolonged. Postmenopausal women have urogenital atrophy with an associated decrease in lubrication. Older women may experience a decline in sexual desire and may require more direct stimulation during sexual

Table 28.4 • Types of Urinary Incontinence

Type	Cause	Symptoms	Treatment Options
Urge incontinence	Detrusor overactivity	Urgency, frequency, nocturia. Loss of small to moderate amounts of urine	Behavioral: bladder training (timed voiding to reduce bladder volume plus urge suppression), elimination of bladder irritants, prompted voiding for cognitively impaired patients, pelvic muscle exercises Pharmacologic: antimuscarinic medications, mirabegron Surgical: intradetrusor botulinum toxin injection, sacral neuromodulation
Stress incontinence	Urinary outlet incompetence from intrinsic urethral sphincter insufficiency or bladder hypermobility	Loss of small amounts of urine associated with transient increases in intra-abdominal pressure (eg, cough, sneeze, laugh)	Behavioral: pelvic floor muscle exercises, weight loss Devices: vaginal cones, urethral plugs, continence pessaries Pharmacologic: No FDA-approved medications for this indication Surgical: urethral sling, tension-free vaginal tape, bladder suspension, injection of periurethral bulking agents
Overflow incontinence	Urinary outlet obstruction or detrusor underactivity	Difficulty emptying bladder, low urine flow, straining to void, urinary dribbling	Treatment depends on cause of obstruction Surgical: relief of bladder outlet obstruction (TURP) Pharmacologic: α-adrenergic antagonists Indwelling or intermittent bladder catheterization

Abbreviations: FDA, US Food and Drug Administration; TURP, transurethral resection of prostate.

activity. Coexisting age-related changes, such as pelvic organ prolapse, osteoarthritis, and incontinence, are important factors affecting sexual function. Lack of an available partner is an important social barrier. Although some decline occurs in the frequency of intercourse among older adults, 50% to 80% continue to be sexually active and report high rates of sexual satisfaction. Clinicians need to be aware that older adults are at risk for sexually transmitted illnesses and to continue to counsel them about preventive strategies.

Medications

Aging affects the 4 principal pharmacokinetic functions. Drug *absorption* may take longer, but the extent of drug absorption is not affected with normal aging. Changes in body composition, including increased adipose tissue and decreased total body water and lean body mass, affect drug *distribution*. For example, lipophilic medications such as diazepam may have a much larger volume of distribution and more prolonged effect. Hepatic *metabolism* of medications decreases with age and disease-related decrease in hepatic perfusion. Finally, drug *elimination* decreases with reductions in renal function. The creatinine serum level is a poor measure of renal function of elderly patients and tends to underestimate the degree of renal insufficiency. Because lean body mass decreases with advancing age, less creatinine is produced. Thus, an older patient who has as much as a 30% reduction in renal function may have a normal serum level of creatinine.

Adverse drug events are common in elderly patients and are a potentially preventable cause of hospital admissions. The most common culprits include warfarin, oral antiplatelet medications, insulin, and oral hypoglycemic medications. A number of established prescribing principles should be considered when caring for older patients (Box 28.8).

Box 28.8 • Principles of Drug Prescription for Older Patients

"Start low and go slow"

Minimize overprescription by frequent review of the patient's medication list

Encourage patients to bring all medications to office visits

Consider medication adverse effects or adverse drug events as a cause of new symptoms that result from altered pharmacokinetics and pharmacodynamics with aging

Avoid prescription of potentially inappropriate medications. Clinical tools such as the 2015 American Geriatrics Society Beers Criteria can help in identifying high-risk medications

KEY FACTS

✓ Hearing loss in older patients—typically multifactorial; may present with social withdrawal or low mood

✓ Poorly fitting appliances (eg, splints, casts) can cause pressure ulcers

✓ Urinalysis should always be part of the workup for incontinence; patients should keep a voiding diary

✓ Bladder training and avoidance of dietary bladder irritants are effective nonpharmacologic therapies for urge incontinence

✓ Asymptomatic bacteriuria is a colonization state and should not be treated

29 Hospital Medicine

DEANNE T. KASHIWAGI, MD; JOHN T. RATELLE, MD

Hospital medicine is the fastest growing medical specialty. It has evolved into a field that focuses on illnesses managed in the inpatient setting. In addition, the practice of hospital medicine requires understanding of operations and care processes specific to the hospital. Hospitalized patients are at risk for such complications as venous thromboembolism (VTE) and hospital-acquired infections. Clinicians who practice hospital medicine must be familiar with the diagnosis, the management, and the prevention of these hospital-acquired conditions. This chapter provides an overview of topics specific to the care of hospitalized patients.

Alcohol and Drug Withdrawal

Alcohol and drug withdrawal is common among hospitalized patients. One in 5 hospitalized adults meet diagnostic criteria for alcohol use disorder, and nearly 1 in 12 adult patients has some degree of alcohol withdrawal while in the hospital. Manifestations of withdrawal can differ widely, from mild symptoms such as anxiety and headache to severe syndromes such as delirium tremens, which has a mortality rate as high as 5%. Effective treatment of alcohol and drug withdrawal involves identification of withdrawal syndromes, assessment of a patient's risk of withdrawal, and selection of appropriate treatments.

KEY FACTS

- ✓ Effective treatment of alcohol and drug withdrawal—involves identification of withdrawal syndromes, assessment of withdrawal risk, and appropriate treatment selection
- ✓ Nutritional and electrolyte deficiencies—common among patients with AWS, and many patients with these deficiencies may require replacement treatments
- ✓ Thiamine deficiency—particularly common among patients with AWS

Alcohol Withdrawal Syndrome

Clinical Features

Symptoms of alcohol withdrawal can begin within as a little as 1 to 2 hours after a patient's last drink and generally follow a pattern that has 4 distinct stages: minor symptoms, hallucinations, alcohol withdrawal seizure, and delirium tremens (Table 29.1). These are collectively called **alcohol withdrawal syndrome** (AWS).

Key Definition

Alcohol withdrawal syndrome: *can begin within 1 to 2 hours after a person's last drink and generally follows a pattern of the distinct stages of minor symptoms, hallucinations, alcohol withdrawal seizure, and then delirium tremens.*

Risk Assessment

For most patients, AWS does not progress beyond stage I (minor symptoms), so it is important to identify which patients are at risk for moderate-to-severe withdrawal and thus will require treatment. The Prediction of Alcohol Withdrawal Severity Scale (PAWSS) (Table 29.2) was created to identify

Table 29.1 • Stages of Alcohol Withdrawal Syndrome[a]

Stage	Typical Onset After Last Drink	Percentage of Patients Who Have This Stage	Hallmark Signs and Symptoms
I Minor symptoms	2-12 hours	100%	Anxiety, tremor, headache, nausea, diaphoresis
II Alcoholic hallucinosis	12-24 hours	20%	Visual, auditory, or tactile hallucinations, or a combination and with normal mentation
III Alcohol withdrawal seizures	24-48 hours	10%	Generalized tonic-clonic seizures
IV Delirium tremens	48-72 hours	5%	Hallucinations with abnormal mentation (ie, delirium), autonomic hyperactivity (eg, hypertension, tachycardia, fever)

[a] Data from Perry EC. Inpatient management of acute alcohol withdrawal syndrome. CNS Drugs. 2014 May;28(5):401-10 and Bayard M, McIntyre J, Hill KR, Woodside J Jr. Alcohol withdrawal syndrome. Am Fam Physician. 2004 Mar 15;69(6):1443-50.

Modified from Mirijello A, D'Angelo C, Ferrulli A, Vassallo G, Antonelli M, Caputo F, et al. Identification and management of alcohol withdrawal syndrome. Drugs. 2015 Mar;75(4):353-65; used with permission.

these patients through a score range from 1 to 10. The PAWSS is designed to be administered during the initial patient evaluation (in the emergency department or hospital ward) and incorporates a patient's history and initial physical findings. Patients with a PAWSS score of 4 or greater are likely to benefit from pharmacologic treatment of AWS.

Treatment

Initial evaluation of a patient with AWS should include a comprehensive history and physical examination, along with a basic laboratory evaluation such as tests for liver function and for serum electrolytes, including magnesium and phosphorus.

Table 29.2 • Prediction of Alcohol Withdrawal Severity Scale (PAWSS)

Parts of PAWSS	Points Awarded
A. Threshold criteria	(1 point either)
1. Have you consumed any amount of alcohol (ie, been drinking) within the past 30 days?	
or Did the patient have a "+" BAL on admission?	________
If the answer to either is ***yes****, proceed with test*	
B. Based on patient interview	(1 point each)
2. Have you *ever* experienced previous episodes of alcohol withdrawal?	______
3. Have you *ever* experienced alcohol withdrawal seizures?	______
4. Have you *ever* experienced delirium tremens?	______
5. Have you *ever* undergone alcohol rehabilitation treatment (ie, inpatient or outpatient treatment programs or Alcoholics Anonymous attendance)?	______
6. Have you *ever* experienced blackouts?	______
7. Have you combined alcohol with other "downers," such as benzodiazepines or barbiturates, during the past 90 days?	______
8. Have you combined alcohol with any other substance of abuse during the past 90 days?	______
C. Based on clinical evidence	(1 point each)
9. Was the patient's BAL on presentation >200?	______
10. Is there evidence of increased autonomic activity (eg, heart rate >120 bpm, tremor, sweating, agitation, nausea)?	______
Total score	______

Abbreviations: BAL, blood alcohol level; bpm, beats per minute.

From Maldonado JR, Sher Y, Ashouri JF, Hills-Evans K, Swendsen H, Lolak S, et al. The "Prediction of Alcohol Withdrawal Severity Scale" (PAWSS): systematic literature review and pilot study of a new scale for the prediction of complicated alcohol withdrawal syndrome. Alcohol. 2014 Jun;48(4):375-90. Epub 2014 Feb 19; used with permission.

Further evaluation may be warranted if there is suspicion that the patient's symptoms are caused by an entity other than an AWS diagnosis.

Nutritional and electrolyte deficiencies are common among patients with AWS, who may require nutrition and electrolyte replacement. Thiamine deficiency is particularly common in AWS. Thiamine administration is recommended in most instances, given its low risk of adverse effects and its potential to prevent Wernicke-Korsakoff syndrome.

Benzodiazepines (BZDs) are the mainstay of AWS treatment and have been shown to reduce symptom severity, symptom duration, and complications such as seizures and delirium tremens. BZDs can be administered as scheduled fixed doses or as part of **symptom-triggered therapy** (STT). STT involves matching the BZD dose and frequency to the AWS severity. The Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar), is an instrument administered by bedside nursing staff to measure AWS severity. The CIWA-Ar quantifies the patient-reported severity of symptoms, including nausea, tremor, and anxiety. A summary score for the CIWA-Ar can be calculated and used to guide the BZD dose as part of STT.

Key Definition

Symptom-triggered therapy: *in alcohol withdrawal syndrome, involves matching benzodiazepine dose and frequency to syndrome severity; is appropriate only for patients with normal mentation who are able to verbalize their symptoms.*

STT is appropriate only for patients with normal mentation who are able to verbalize their symptoms.

For patients with severe withdrawal symptoms or at high risk for severe withdrawal (eg, history of seizures or delirium tremens), BZDs should be administered regardless of the CIWA-Ar score.

Adjunctive therapies for AWS may include 1) clonidine to treat hypertension and tachycardia related to autonomic hyperactivity and 2) antipsychotics to treat hallucinations and agitation. Patients having severe symptoms despite BZD therapy should be transferred to the intensive care unit for consideration of parenteral infusions, such as dexmedetomidine, propofol, or barbiturates. Non-BZD medications, such as gabapentin and baclofen, can be considered for mild withdrawal but should not replace BZDs for AWS severe enough to necessitate hospitalization.

KEY FACTS

- ✓ Benzodiazepines—mainstay treatment of AWS and which reduce symptom severity, symptom duration, and complications
- ✓ Adjunctive therapies for AWS—clonidine for hypertension and tachycardia related to autonomic hyperactivity and antipsychotics for hallucinations and agitation
- ✓ STT is appropriate only for patients with normal mentation who can verbalize their symptoms
- ✓ BZDs should be administered to patients with severe withdrawal symptoms or at high risk for severe withdrawal, regardless of their CIWA-Ar score

Opioid Withdrawal

Clinical Features

Withdrawal related to opioid interruption can begin within hours (for short-acting opioids or heroin) to days (for long-acting opioids, such as methadone). Characteristics include dysphoria, piloerection, rhinorrhea and lacrimation, mydriasis, myalgias, nausea and vomiting, and abdominal cramping and diarrhea. **Opioid withdrawal** in the hospital can be precipitated by reversal with use of an opioid antagonist (eg, naloxone).

For patients taking long-term opioid therapy, withdrawal caused by opioid antagonists can be associated with an acute and severe rise in catecholamine levels, which can lead to autonomic hyperactivity and, in rare instances, cardiac arrest. Therefore, opioid antagonists should be used with caution for patients receiving long-term opioid therapy.

Key Definition

Opioid withdrawal: *begins within hours to days after opioid interruption and can include dysphoria, piloerection, rhinorrhea, mydriasis, myalgias, nausea, vomiting, and abdominal cramping.*

Treatment

First-line medications to treat opioid withdrawal are opioid agonists, such as methadone and buprenorphine. Second-line medications are central α-2 agonists, such as clonidine or lofexidine.

Adjunctive medications can be used to treat specific withdrawal symptoms, such as nausea (promethazine), diarrhea (loperamide), myalgias (ibuprofen and acetaminophen), and abdominal cramping (dicyclomine).

BZD Withdrawal

Clinical Features

Withdrawal from BZD use can result in such signs and symptoms as anxiety, insomnia, agitation, perceptual changes, and seizures. The onset of withdrawal may appear as early as 24 to 48 hours after cessation of short-acting BZDs (eg, alprazolam, temazepam, oxazepam) and as late a week or more for long-acting BZDs (eg, clonazepam, diazepam, chlordiazepoxide).

Treatment

Treatment of BZD withdrawal typically involves titration of a long-acting BZD to control symptoms, followed by prolonged taper over a course of several weeks to months. The rapidity of the taper should be individualized and often is conducted under the supervision of a psychiatrist or an addiction specialist.

Stimulant Withdrawal

Clinical Features

Drug withdrawal can occur after cessation of either prescription (eg, methylphenidate, dextroamphetamine) or nonprescription (eg, cocaine, amphetamine) stimulants and is associated with irritability, anxiety, depression, and hypersomnolence. Symptoms of stimulant withdrawal typically begin within 24 hours of cessation, but the onset, severity, and duration of withdrawal can differ widely, depending on the intensity and chronicity of stimulant use.

Treatment

In most instances, symptoms resolve within 3 to 5 days and require only supportive care. Yet, some patients have severe depression, paranoia, or psychosis, or a combination. Patients with any of these symptoms should be monitored and evaluated for risk of harm to themselves or others.

Health Care–Associated Infections

Of hospitalized patient, 4% are treated for a hospital-acquired infection. The most common of these infections are pneumonia and surgical site infections (SSIs), followed by infections of the gastrointestinal tract, urinary tract, and bloodstream. **Device-associated infections** (ie, central line–associated bloodstream infection [CLABSI], catheter-associated urinary tract infection [CAUTI], and ventilator-associated pneumonia [VAP]) account for 25.6% of hospital-acquired infections. These 3 infection types are preventable.

KEY FACTS

- ✓ Health care–associated infections—examples are pneumonia, SSI, and *Clostridioides difficile* gastrointestinal tract infection
- ✓ Ventilator-associated pneumonia—occurs more than 48 hours after endotracheal intubation
- ✓ Hospital-acquired pneumonia—not present at admission but develops more than 48 hours after it
- ✓ Surgical site infection—prevention step is IV antibiotic prophylaxis

Key Definition

Device-associated infections: *central line–associated bloodstream infection, catheter-associated urinary tract infection, and ventilator-associated pneumonia.*

Hospital-Acquired Pneumonias

Hospital-acquired pneumonia (HAP) and VAP account for 21.8% of all hospital-acquired infections.

Diagnosis

A gold standard has yet to be established for the diagnoses of HAP and VAP. Pneumonia is considered among patients with a new lung infiltrate and clinical signs of infection (eg, leukocytosis, fever, purulent sputum, hypoxia). HAP is not present on patient admission; it develops more than 48 hours after admission. By comparison, VAP occurs more than 48 hours after endotracheal intubation.

Noninvasive sputum samples obtained through spontaneous expectoration, induced sputum, nasotracheal suctioning, or endotracheal aspiration (for patients receiving ventilator assistance) are sent for culture to determine the pathogens responsible for hospital-acquired pneumonias.

Treatment

Empirical therapy for HAP and VAP is based on local resistance patterns published in hospital antibiograms and the presence of risk factors for multidrug-resistant (MDR) organisms.

Intravenous (IV) antibiotic use within the prior 90 days is a risk factor for MDR organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*. Risk factors for MDR VAP are IV antibiotics within the prior 90 days, septic shock and acute respiratory distress syndrome, hospitalization of 5 days or longer, and acute renal replacement therapy that precedes VAP.

Pseudomonas should be double-covered (ie, a β-lactam antibiotic and a non–β-lactam antipseudomonal antibiotic) for patients with VAP who have risk of antibiotic resistance; are hospitalized where more than 10% of the gram-negative isolates are resistant to any antibiotic being considered for monotherapy; or are hospitalized where antibiotic susceptibility rates are unavailable.

Patients with HAP and underlying structural lung disease, such as bronchiectasis or cystic fibrosis, should receive *Pseudomonas* double-coverage therapy. HAP and VAP each should be treated with antibiotics for 7 days.

VAP therapy includes vancomycin for MRSA coverage. It also provides double-coverage for *Pseudomonas*, with an antipseudomonal non–β-lactam and antipseudomonal β-lactam antibiotic (ie, piperacillin/tazobactam, cefepime, ceftazidime, imipenem, meropenem, or the monobactam aztreonam). The indicated non–β-lactam antibiotics are the fluoroquinolones ciprofloxacin and levofloxacin; aminoglycosides, including amikacin, gentamicin, and tobramycin; and polymyxins, including colistin and polymyxin B.

HAP therapy is summarized in Figure 29.1.

Prevention

Mechanical ventilation inherently places patients at risk for VAP. Preventative measures against VAP include interventions to decrease the duration of mechanical ventilation (Table 29.3).

Surgical Site Infections

Although antimicrobial prophylaxis decreases SSI risk, the SSIs continue to be among the most common hospital-acquired infections.

Diagnosis

Superficial SSIs occur within 30 days after surgical procedures and involve skin or subcutaneous tissue. They also have at least 1 of the following characteristics: purulent drainage; positive fluid or tissue cultures from the incision; pain or tenderness; swelling; or redness or heat. In addition, a surgeon may deliberately open an incision when either the wound is not cultured or the culture results show positivity.

Deep SSIs occur within 30 days after the operation if no implant is left in place or within 12 months if an implant is present. In deep SSI, the diagnosis requires 1 or more of the following: purulent drainage from the incision; an abscess; a diagnosis of deep SSI by a surgeon or the attending physician; or the spontaneous dehiscence of the incision. In addition, a surgeon may deliberately open the incision 1) when the wound has positive cultures or 2) when no cultures are sent and the patient has fever or pain, and from this symptom, the diagnosis can be reached.

Treatment

The most common organisms to cause SSIs after clean procedures, in which the respiratory tract, gastrointestinal tract, and genital tract are not entered, are *S aureus* and coagulase-negative staphylococci. In clean-contaminated procedures such as abdominal operations, the most common causes of SSI are gram-negative bacilli, enterococci, and skin flora.

Prevention

The IV antibiotic prophylaxis helps prevent SSIs for patients having a surgical procedure. The first dose of prophylactic antibiotic is given within 60 minutes before surgical incision.

Typically, first- or second-generation cephalosporins are used for SSI prophylaxis. Vancomycin is reserved for patients with a β-lactam allergy.

Central Line–Associated Bloodstream Infection

Cases of CLABSI account for 84% of hospital-acquired primary bloodstream infections.

Diagnosis

Blood for cultures is drawn before antibiotic therapy for patients with suspected CLABSI. The diagnosis of CLABSI is made when 1) the same organism involved in the infection also grows from the catheter tip and at least 1 percutaneous blood culture or 2) in comparison of 2 blood cultures—1 drawn from the catheter and 1 from a peripheral vein—the microbial colony count is 3 or more times greater from the catheter than the periphery or the catheter cultures show positivity at 2 or more hours before the peripheral cultures turn positive.

Treatment

The most common pathogens to cause CLABSI are coagulase-negative staphylococci, *S aureus, Candida* species, and enteric gram-negative bacilli.

Vancomycin is given empirically in areas with high MRSA prevalence. Coverage for gram-negative bacilli with a fourth-generation cephalosporin, carbapenem, or a combined β-lactam and β-lactamase is based on local antibiogram data and illness severity.

Antibiotic therapy for patients with neutropenia or sepsis includes *P aeruginosa* coverage.

An antibiotic lock therapy to salvage a central venous catheter is considered for patients with long-term venous catheters, with no sign of tunnel or exit site infections, and with CLABSI not due to *S aureus* or *Candida* species. Lock therapy is used in conjunction with systemic antibiotics.

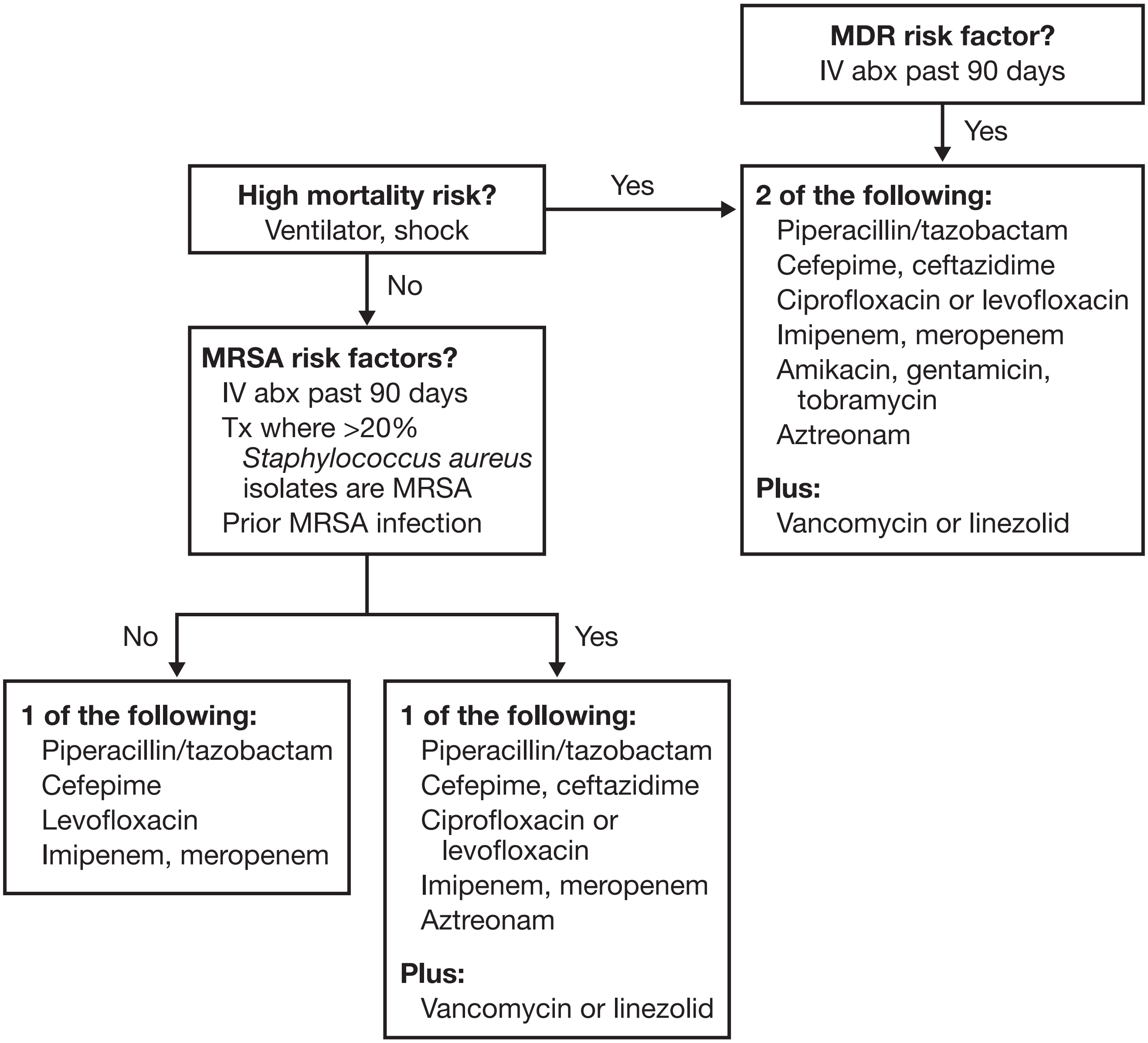

MDR risk factor?
IV abx past 90 days
Yes
High mortality risk?
Ventilator, shock
Yes
2 of the following:
Piperacillin/tazobactam
Cefepime, ceftazidime
Ciprofloxacin or levofloxacin
Imipenem, meropenem
Amikacin, gentamicin, tobramycin
Aztreonam
Plus:
Vancomycin or linezolid
No
MRSA risk factors?
IV abx past 90 days
Tx where >20% *Staphylococcus aureus* isolates are MRSA
Prior MRSA infection
No
Yes
1 of the following:
Piperacillin/tazobactam
Cefepime
Levofloxacin
Imipenem, meropenem
1 of the following:
Piperacillin/tazobactam
Cefepime, ceftazidime
Ciprofloxacin or levofloxacin
Imipenem, meropenem
Aztreonam
Plus:
Vancomycin or linezolid

Figure 29.1. *Treatment of Hospital-Acquired Pneumonia. Abx indicates antibiotics; IV, intravenous; MDR, multidrug-resistant; MRSA, methicillin-resistant* Staphylococcus aureus*; tx, treatment.*

Data from Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Executive Summary: Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016 Sep 1;63(5):575-82.

Table 29.3 • Prevention Strategies for Hospital-Acquired Infections

VAP	CLABSI	CAUTI	*Clostridioides difficile* Infection
Avoid intubation and use noninvasive positive pressure ventilation when possible Minimize sedation Maintain or improve physical conditioning Change ventilator circuits only when soiled or malfunctioning Elevate the head of the bed to 30° to 45°	Before central venous catheter insertion, closely consider its indication Provide clinician education on insertion, care, and maintenance of central lines Use central line insertion checklists Perform adequate hand hygiene before catheter insertion Disinfect catheter hubs, connectors, and ports before accessing the line Remove nonessential central lines	Place urinary catheter only when indicated Remove urinary catheter as soon as it is no longer needed Use a closed catheter system	Use antibiotic stewardship Follow contact precautions at least until diarrhea stops Follow hand hygiene and barrier precautions Use single-use disposable equipment Dedicate nondisposable equipment to the patient's room Use *C difficile* sporicidal or 5,000-ppm chlorine cleaning agents

Abbreviations: CAUTI, catheter-associated urinary tract infection; CLABSI, central line–associated bloodstream infection; ppm, parts per million; VAP, ventilator-associated pneumonia.

KEY FACTS

- ✓ Central line–associated bloodstream infection—suspected when blood cultures grow *Staphylococcus aureus, Candida* species, or coagulase-negative staphylococci
- ✓ Strategies to prevent CLABSI—close consideration of the central venous catheter indication and central line removal as soon as the patient no longer needs the catheter
- ✓ Vancomycin—empirical administration for CLABSI in areas with high prevalence of MRSA

Prevention

Prevention strategies against CLABSI include close consideration of the central venous catheter indication and removal of the central catheter as soon as the patient no longer needs it (Table 29.3).

Catheter-Associated Urinary Tract Infections

CAUTIs account for 67.7% of hospital-acquired urinary tract infections (UTIs).

Diagnosis

Signs and symptoms that suggest UTI in a catheterized patient include fever, rigors, acute encephalopathy, malaise, lethargy, hematuria, pelvic and flank pain, and costovertebral angle tenderness. A catheter urine specimen, or a mid-stream specimen if the catheter has been removed within the previous 48 hours, is collected to test for CAUTI. Screening for catheter-associated asymptomatic bacteriuria is not recommended.

CAUTI is diagnosed for patients who have indwelling or suprapubic catheters or require intermittent catheterization, with signs or symptoms of urinary tract infection and a 10^3 cfu/mL bacteria concentration or greater. Pyuria in a catheterized patient is not diagnostic of CAUTI.

KEY FACTS

- ✓ Catheter-associated urinary tract infections—account for 67.7% of hospital-acquired UTIs
- ✓ Signs and symptoms suggestive of UTI in catheterized patients—include fever, rigors, acute encephalopathy, malaise, lethargy, hematuria, and pelvic and flank pain

Treatment

Antibiotic therapy should be guided by urine culture results because CAUTIs are often caused by MDR bacteria. For patients with CAUTI, indwelling catheters should be changed after they are in place for longer than 2 weeks. CAUTI is treated for 7 days if symptoms quickly resolve or for 10 to 14 days if they do not resolve quickly.

Prevention

Duration of catheterization is the biggest risk factor for CAUTI. Acceptable reasons to place a catheter should be considered before insertion and include urinary retention, urinary incontinence, need to accurately measure urine output, and situations where a patient may be unable to collect urine (eg, with general anesthesia for a prolonged surgery) (Table 29.3).

Clostridioides difficile Infection

Clostridioides difficile (formerly known as *Clostridium difficile*) accounts for 70.9% of hospital-acquired gastrointestinal tract infections.

Diagnosis

Patients without diarrhea should not have stool tested for *C difficile*. Polymerase chain reaction tests for *C difficile* toxins are superior to toxins A + B enzyme immunoassay testing.

Treatment

Treatment is guided by disease severity and whether the ***C difficile* infection** (CDI) recurs (Table 29.3).

If a patient's condition does not improve within 5 to 7 days of metronidazole therapy, treatment should be switched to vancomycin. Antiperistaltic medications are used sparingly, if at all, for patients with CDI. Patients with complicated CDI and without treatment response should have computed tomography of the abdomen and pelvis and a surgical consultation.

Prevention

Antibiotic stewardship reduces CDI risk. Additional infection control precautions limit the spread of CDI after it is diagnosed in a care facility (Table 29.3).

Needlestick Injuries

Health care workers are at risk for exposure to bloodborne pathogens through blood and body fluids, including needlestick injury (NSI). Prevention of NSI is the best way to avoid occupational bloodborne pathogen infections, but if an NSI occurs, the injury should be washed immediately with soap and running water. Risk of transmission of HIV is 0.3%;

hepatitis C virus (HCV), 1.8%; and hepatitis B virus (HBV), approximately 30%.

After an NSI, the source patient is assessed for HBV, HCV, and HIV infection as soon as possible. Postexposure prophylaxis for HIV should not be delayed while waiting for test results. If the source patient tests negative for HIV, postexposure prophylaxis can be discontinued for the health care worker. If the test is positive, the worker should continue to take emtricitabine, tenofovir, and raltegravir for 4 weeks.

HBV postexposure prophylaxis is not given after an NSI to a health care worker if the source patient tests negative for hepatitis B surface (HBs) antigen (HBsAg). If the patient is positive for HBsAg and the health care work has not been vaccinated previously, hepatitis B immune globulin is administered once and the HBV vaccination series started. If the worker has responded to prior vaccination (anti-HBs ≥10 mIU/mL), no treatment is required. If the worker is a nonresponder (anti-HBs <10 mIU/mL), hepatitis B immune globulin is given once and the HBV vaccination started or the immune globulin is given twice.

Postexposure prophylaxis is not administered for HCV infection after NSI. The source patient should be tested for anti-HCV. If the patient tests positive, the exposed health care worker should have anti-HCV and alanine aminotransferase tests at baseline and at 4 to 6 months later to monitor for HCV infection.

Venous Thromboembolism

VTE can be a major cause of morbidity and death among medical inpatients, and its occurrence is considered a “never” event by agencies such as the Centers for Medicare and Medicaid Services. Prevention of VTE involves risk assessment followed by appropriate pharmacologic or nonpharmacologic therapy.

Risk Assessment

Risk factors for VTE include the extrinsic risk factors (eg, immobilization, hormonal medications, recent surgery or trauma), the intrinsic risk factors (eg, advanced age, active cancer, thrombophilia, inflammatory bowel disease, heart or respiratory failure), and the risk factors related to acute illness (eg, acute infection, myocardial infarction, stroke). VTE incidence differs greatly—from less than 1% among low-risk persons to more than 10% among high-risk persons.

Risk assessment models should be used to stratify a patient’s risk (ie, low vs high) of VTE while hospitalized. Example risk assessment models for nonsurgical hospitalized adults are the Padua prediction score and the IMPROVE score.

Prevention

Prevention of VTE among nonsurgical hospitalized adults may include either pharmacologic or nonpharmacologic methods. The choice of prevention methods should be based on the risk of VTE vs the risk of bleeding.

Medical inpatients at high risk for VTE should receive pharmacologic prevention in the form of subcutaneous unfractionated heparin, low-molecular-weight heparin, or fondaparinux. Medical inpatients at low risk for VTE should not receive pharmacologic prevention.

The medical inpatients who have active bleeding or are at high risk for bleeding should not receive pharmacologic prevention but should receive nonpharmacologic prevention in the form of intermittent pneumatic compression devices or graduated compression stockings.

The risk of VTE may extend beyond the acute inpatient stay for some hospitalized adults. Yet, the role of VTE prevention after the hospitalization is unclear.

Nonsurgical adult inpatients should not receive VTE prevention, pharmacologic or nonpharmacologic, after they are discharged from the hospital.

Key Definition

Transitions of care: *comprise the communication and processes that occur when care providers transfer responsibility for a patient’s treatment.*

Transitions of Care

Transitions of care comprise the communication and processes that occur when care providers transfer responsibility for a patient’s treatment. These handoffs of care occur 1) when a patient changes physical locations, such as from 1 unit to a different unit in a hospital or the transition from hospital to home, and 2) when a provider changes a shift either daily or at the end of a series of days spent caring for the patient.

Such care transitions put patients at risk for adverse events. Recommendations for transitions of care between providers at the end of their shift include a verbal and interactive handoff process, during which the sickest patients are discussed first. The verbal handoff should be supplemented with a written component. Handoffs of care when patients transition from the hospital should prioritize medication reconciliation, follow-up plans, and postdischarge contingency education.

30

Medical Ethics[a]

JON C. TILBURT, MD; C. CHRISTOPHER HOOK, MD

Medicine is first and foremost a relationship—a coming together of a patient who is ill or has specific needs and a physician whose goal is to help the patient. The physician-patient relationship is a *fiduciary* relationship. Physicians have knowledge, skills, and privileges that patients do not have. In turn, patients trust that physicians act in the patients' best interests.

Such connections involve medical ethics—a set of principles and systematic methods that guide physicians on how they ought to act in their relationships with patients and how to resolve moral problems that arise in the care of patients. These principles and methods are based on moral norms shared by both the lay society (which may differ from culture to culture) and the medical profession. Advances in medical science and the ever-developing social and legal milieu result in dynamic changes, challenges, and ethical dilemmas in medical practice.

An **ethical dilemma** occurs when conflicting moral principles have no clear course to resolve a problem (ie, credible evidence exists both for and against a certain action).

Principles of Medical Ethics

A widely used framework for medical ethics is principalism. This framework delineates 4 principles that can help categorize the norms that are at stake in the ethical requirements and challenges that arise in practice. These principles (in no specific order) are **beneficence**, the duty to do good; **nonmaleficence**, to prevent harm; **respect for patient autonomy**, to respect persons and their rights of self-determination; and **justice**, to treat patients fairly (free of bias and on the basis of medical need).

The principles are considered *prima facie*—that they are valid in most situations—but the priority of each principle can change on a case-by-case basis. In clinical practice, these principles can be at odds with each other. For example, a beneficent physician may recommend an intervention that has minimal risk of harm. However, a patient may exert the patient's autonomy and decline the procedure.

Although beneficence is a primary motivating ethical principle for most physicians, the other principles contextualize, constrain, and inform the orientation of physicians to accomplish the good (Figure 30.1).

Key Definitions

Ethical dilemma: *occurs when conflicting moral principles have no clear course to resolve a problem (ie, credible evidence exists both for and against a certain action).*

Beneficence: *the duty to do good.*

Nonmaleficence: *the duty to prevent harm.*

Respect for patient autonomy: *the duty to respect persons and their rights of self-determination.*

Justice: *the duty to treat patients fairly (ie, free of bias and based on medical need).*

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[a] Portions previously published in Mueller PS, Hook CC, Fleming KC. Ethical issues in geriatrics: a guide for clinicians. Mayo Clin Proc. 2004 Apr;79(4):554-62; used with permission of Mayo Foundation for Medical Education and Research.

The editors and authors acknowledge the contributions of Keith M. Swetz, MD, to the previous edition of this chapter.

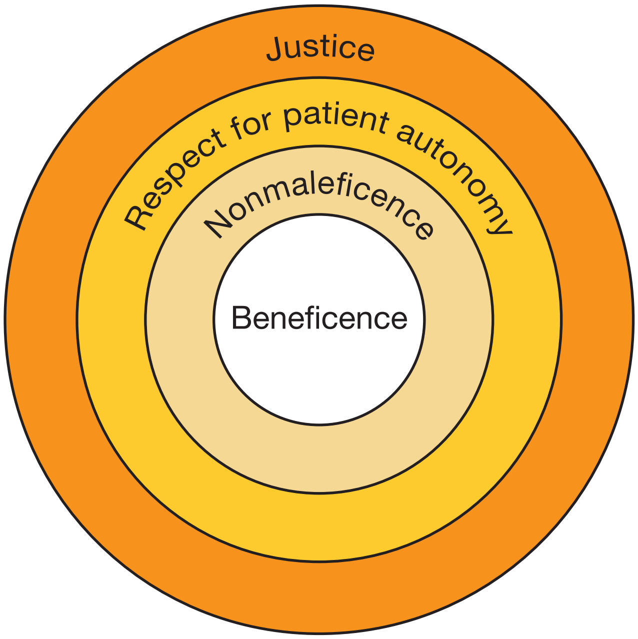

Figure 30.1. *The 4 Principles of Medical Ethics.*

Beneficence

Beneficence is action to benefit patients through preserving life, restoring health, relieving suffering, and restoring or maintaining function. Physicians must pursue the benefit of the patient. That benefit involves the medical definition and each patient's self-definition of *good*. This principle may be viewed on several levels of benefit, including how an intervention may benefit the patient 1) biomedically or physiologically, 2) personally (eg, waiting for family to arrive before withdrawal of a ventilator), or 3) ultimately (ie, in respect to a patient's belief system or world view).

Nonmaleficence

Nonmaleficence couples closely with beneficence and requires that physicians minimize harm or the risk of harm to patients. The principle has roots in the Hippocratic corpus: "As to diseases, make a habit of 2 things: to help, or at least do no harm." This principle also addresses unprofessional behavior, such as verbal, physical, and sexual abuse of patients or uninformed and undisclosed interventions or experimentation on patients. Practical examples are listed in Box 30.1.

Respect for Patient Autonomy

The word *autonomy* derives from the Greek words *auto* (self) and *nomos* (rule). Respect for autonomy is rooted in deep notions of respect for the integrity and dignity of individuals. In earlier renditions of principlism, this principle was referred

Box 30.1 • Practical Applications of Nonmaleficence in Clinical Practice

Practical Applications of Nonmaleficence in Clinical Practice

Nonabandonment—an ethical obligation to provide ongoing medical care after the patient and physician mutually concur to enter into an alliance

Nonabandonment is closely related to the principles of beneficence and nonmaleficence and is fundamental to the long-term physician-patient relationship

Patient nonadherence, in terms of taking medications or following a physician's instructions, is not grounds for abandonment

A physician should strive to respond to a patient's needs over time but in the process should not trespass the physician's own values

Conflict of interest—an ethical obligation to refrain from activities that are not in patients' best interests

Such conflicts of interest may unduly influence physicians' practices (eg, prescription, ordering of tests, therapeutic recommendations)

For example, acceptance of a gift from a representative of a pharmaceutical company constitutes a conflict of interest if the physician who accepts the gift also writes prescriptions for drugs manufactured by that company

Physician impairment—according to the American Medical Association, an impaired physician is someone who is "unable to practice medicine with reasonable skill and safety to patients because of physical or mental illness, including deteriorations through the aging process, or loss of motor skill, or excessive use or abuse of drugs including alcohol"

Impairment is distinct from competence, which specifically concerns the physician's knowledge and skills to adequately perform health care duties as a physician. Impairment and incompetence both may compromise patient care and safety

Physicians have a moral, professional, and legal obligation to report impaired and incompetent colleagues to the appropriate authority. Specifics of reporting differ by state, but all states have a reporting requirement

Typical authorities to contact about physician impairment include the institutional chief of staff or impairment program, local or state medical society impairment programs, or the state licensing body. Report of the behavior of a colleague must be based on objective evidence rather than supposition

Double effect—the pursuit of beneficence may lead to unintended injury or death. Use of palliative sedation and analgesia for terminally ill patients is discussed more fully in Chapter 33, "Palliative Care" to as *respect for persons*. For patients to be fully autonomous, an ideal that no one can fully achieve, the patients must 1) be informed (see the Informed Consent and Exceptions section), 2) have liberty (be free from coercion or duress and have the opportunity to influence the courses of their life and medical treatment), and 3) have decision-making capacity. Of note, decision-making capacity is not the same as the legal term *competence*. **Decision-making capacity** is a physician's clinical determination of a patient's ability to understand the situation and make appropriate decisions for treatment. **Competence** is the legal determination and status that a person has the right to make life-affecting decisions (not only health-related decisions but also, for example, financial decisions).

Key Definitions

Decision-making capacity: *a physician's clinical determination of a patient's ability to understand the patient's situation and to make appropriate decisions for treatment.*

Competence: *legal determination and status that a person has the right to make life-affecting decisions.*

In clinical practice, the lack of decision-making capability should be demonstrated, not presumed. Confusion, disorientation, psychosis, and other cognitive changes caused by diseases, metabolic disturbances, and medical interventions can affect decision-making ability for a specific decision. Decisionally capable patients have the right to refuse all medical interventions (Box 30.2).

KEY FACTS

- ✓ Principalism—a widely used framework for medical ethics
- ✓ Four principles encompass most clinical ethical concerns—beneficence, nonmaleficence, respect for patient autonomy, and justice
- ✓ Physicians are ethically obligated to avoid activities not in patients' best interests
- ✓ Physician impairment—due to physical or mental illness, loss of motor skill, or drug use or abuse; distinct from incompetence
- ✓ Pursuit of beneficence—may have a double effect, leading to unintended injury or death

Box 30.2 • Clinical Standards to Assess Decision-making Capacity

The patient can make and communicate a choice

The patient understands the medical situation and prognosis, the nature of the recommended care, and the available alternative options and the risks, benefits, and consequences of each

The patient's decisions are stable over time

The decision is consistent with the patient's values and goals

The decision is not due to delusions or altered mental status

The ethical principle of respect for patient autonomy and numerous court decisions—from the Quinlan case (1976) and Cruzan case (1990) to the Schiavo case (2005)—have established a patient's right to refuse medical treatment, even if death inevitably follows such a refusal.

Promotion and Preservation of Patient Autonomy

Physicians commonly care for patients who lack decision-making capacity or lose the capability over time. To preserve their autonomy, the patients who lose this capacity nonetheless may express their wishes through 2 means: an advance directive and surrogate decision makers. These means are discussed, along with futility and demands for nonbeneficial interventions, in Chapter 33, "Palliative Care."

Informed Consent and Exceptions

A derivative of the principle of respect for patient autonomy (and nonmaleficence) is informed consent (and refusal)—the voluntary acceptance (or refusal) of physician recommendations by decisionally capable patients or their surrogates who have received sufficient information regarding the risks, benefits, and alternatives to the proposed interventions. Three elements are required for informed consent: patient decision-making capacity, patient voluntariness, and patient or surrogate receipt of accurate and sufficient information from which to make a decision. The amount of information shared with the patient should be guided not only by what the physician believes is adequate (professional practice standard) but also by what the average prudent person needs to make an appropriate decision (the so-called reasonable person standard). Discussion of available alternatives to the proposed treatment, including doing nothing, should be included.

During shared decision making, the physician should present to the patient the recommendations that the patient can accept or reject. Shared decision making reminds physicians that it is not their job just to inform but also to invest their benevolent motivations and offer a recommendation. Simply laying out a menu of choices may lead to confusion or the perception by the patients that the physician is unconcerned with their welfare. If a patient refuses the recommended treatment and chooses one of the alternatives, the patient's physician should respect this choice. The final plan should reflect an agreement between a well-informed patient and a well-informed, sympathetic, and unbiased physician.

In rare exceptions, a physician can treat a patient without informed consent (eg, to treat an emotionally unstable patient who requires urgent care, to inform an emotionally unstable patient of details that may produce further problems). The principle of implied consent is invoked when true informed consent is not possible because the patient (or the surrogate) is unable to express a decision about treatment. This situation often occurs in emergencies, in which physicians are compelled to provide immediate medically necessary therapy, without which harm would result. Implied consent and duty to assist a person in urgent need of care have been accepted legally (eg, Good Samaritan laws) and provide the physician a legal defense against battery (although not against negligence).

Truth Telling and Therapeutic Privilege

The physician must provide a decisionally capable patient with truthful information to assist the patient in making informed medical decisions. Without receipt of sufficient, accurate, and true information, patients cannot make autonomous decisions. Occasionally, a physician may withhold part or all of the truth if the physician believes that telling the truth is highly likely to cause considerable psychological injury, a concept known as *therapeutic privilege*. The decision for intentional nondisclosure must be recorded fully in the health record. Although invocation of therapeutic privilege may be ethically justified in some circumstances, legal protection is not guaranteed for less-than-full disclosure.

Some decisionally capable patients may forgo complete disclosure, deferring the receipt of information and decision making to other persons. Waiver of complete disclosure may occur by individual preference or in the context of cultural norms. Regardless, this preference should be respected as the patient's autonomous choice if care teams are confident the choice is an authentic expression of the patient's preference.

Medical Errors

Errors committed in the course of treatment require full and honest disclosure because patients deserve to know the truth about what has happened. Frank disclosure helps to preserve or restore trust, or both, in the physician-patient relationship. Physicians often fear that if they disclose errors, they will be sued. However, the opposite is more often true. A patient is more likely to pursue legal action if the patient suspects something has gone awry or the physician subsequently discovered the error but did not tell the patient. Studies have shown that in many cases, patients sue physicians primarily to discover the truth.

Confidentiality

Privacy is integral to the respect of a person and to protect an individual's autonomy. Confidentiality respects the right to privacy. In medicine, it provides the patient with security to keep sensitive, personal information within the realm of the physician-patient relationship. The physician is ethically and legally obliged to maintain a patient's health information in strict confidence, a tradition dating to the adoption of the Hippocratic Oath in 1948. Ensurance of confidentiality encourages complete communication of all relevant information that may affect the patient's health. If a physician foregoes documentation of relevant clinical information because a patient requests the waiver, the physician compromises safety and quality. Such a request should not be accommodated.

However, the obligation to protect patients may be overridden when serious bodily harm to a patient or other persons may result if reasonable steps are not taken. In some instances, a patient's data must be shared with public health care agencies. Examples are documentation of certain infectious diseases, physical abuse, or gunshot wounds and concerns for the public health and welfare. State-to-state variability exists in reporting requirements, and physicians should be aware of the local statutes.

Conscientious Objection

Another conflict between a patient and a physician (and other health care providers) occurs when a patient requests an intervention that may be sanctioned legally but is morally unacceptable to the physician. In this situation, the ethical issue centers on moral acceptability of the intervention and not on efficacy. An objector may believe so strongly against the permissibility of the specific intervention that the objector considers the intervention as commission of evil.

Historically, and dating to the Hippocratic Oath, medical ethics principles have recognized that physicians, in their obligations to protect life, may conscientiously object to acts involving the deliberate taking of human life. Many states have so-called conscience laws that protect health care providers from being forced to be complicit in acts that would violate their conscience.

What constitutes an issue of conscience? In medicine, the issue of objection must be in regard to a specific act in all circumstances. Claims of conscience regard acts, not persons. A claim that intrinsically involves discrimination against a given person (eg, the person's race, color, sexual preference, nationality, religion) is not legitimate and violates the principle of justice (see the Justice section). Furthermore, the conscientious objector is restricted to forgo participation in only the specific objectionable act, not in the provision of the rest of the patient's care. To do otherwise would be an act of abandonment. For example, a physician may refuse to participate in an abortion (including provision of anesthesia and those actions directly and immediately involved in the act), but the physician may not decline postoperative care of the patient who has complications from the procedure.

A conscientious objector has the right to decline participation in the requested intervention. However, the conscientious objector should not berate the patient or obstruct the patient from receipt of the intervention from other health care providers. Health care organizations may legitimately expect the physician to refer the patient to another provider or at the least to an institutional resource that can assist the patient in securing legally sanctioned interventions. Such resources include a patient affairs officer or an administrator.

KEY FACTS

- ✓ Decision-making capacity—determined by the physician and not to be confused with competence, which is a legal determination
- ✓ A patient's decision-making capacity needs to be demonstrated; incapacity should not be presumed
- ✓ Informed consent has 3 required elements—patient decision-making capacity, patient voluntariness, and provision of accurate and sufficient information to the patient
- ✓ If a patient requests an intervention that a physician finds morally objectionable, the physician can refuse that intervention but cannot abandon the patient or refuse to provide other care

Justice

The principle of justice expresses that every patient deserves optimal care and must be provided optimal care fairly and as warranted by the underlying medical condition and within the constraints of available resources. The identification of optimal medical care should be based on the patient's health care need and the perceived clinical benefit to the patient. A patient's social status, ability to pay, or perceived social worth should not dictate the quality or quantity of medical care. A physician's clear-cut responsibility is to a patient's well-being (beneficence). Physicians should not make decisions about individual patient care on the basis of larger societal needs, because the bedside is not the place for general policy decisions. Doing so is unlikely to achieve overall fairness. Nevertheless, physicians should be conscious of larger societal needs and should be leaders in the development of fair policies to regulate the allocation of scarce or costly resources. These endeavors should take place away from the bedside and the individual physician-patient relationship.

Ethics, Law, and Death

Definition of Death

Death is the irreversible cessation of circulatory and respiratory functions or the irreversible cessation of all functions of the entire brain, including the brainstem. Clinical criteria (at times supported by electroencephalographic testing or assessment of cerebral perfusion) permit a reliable diagnosis of brain death.

Key Definition

Death: *the irreversible cessation of circulatory and respiratory function or of all functions of the entire brain, including the brainstem.*

A patient's family should be informed of brain death of the patient but should not be asked to decide whether medical therapy should be continued. One exception is when the patient's surrogate (or the patient through an advance directive) permits certain decisions, such as organ donation, in the case of brain death.

After brain death is ascertained and no further therapy can be offered, the primary physician—preferably after consultation with another physician involved in the patient's care—may withdraw supportive measures. This approach is accepted throughout the United States, with the exception of the states that have modified their definition-of-death statutes to allow a religious exemption for groups (eg, Orthodox Jews) that do not accept brain death as a valid criterion for death. In these states, continued care may be requested of the caregivers until circulatory and respiratory functions collapse.

Physician-Assisted Death

All 4 principles of medical ethics have an effect on the issue of physician aid in dying (previously referred to as *physician-assisted suicide*) and euthanasia. Historically, the medical profession has taken a strong stand against physicians directly killing patients. Yet, this prohibition has been challenged on the basis of patient autonomy, beneficence, or compassion and of other grounds. The American Medical Association, the American College of Physicians, and certain other large professional medical groups have maintained a stance against physician aid in dying and euthanasia.

In 1997, the US Supreme Court ruled that states may maintain laws prohibiting euthanasia and physician aid in dying, but states also may pass laws allowing these practices. Although the Court did not find a right to physician-assisted death, it emphasized a patient's right to adequate, aggressive pain control, even if it might shorten the patient's life. In 1997, the people of Oregon reiterated their support for physician aid in dying by reapproving a referendum that legalized physician aid in dying but prohibited euthanasia. The Oregon law requires that in such cases, the patient 1) has a terminal condition, 2) is decisionally capable, 3) has initiated 2 verbal requests and 1 written request for a prescription for a lethal overdose, 4) undergoes a second-opinion consultation, 5) receives appropriate psychiatric intervention if perceived to be depressed, and 6) has a 15-day waiting period after the request has been made to allow a change of the patient's mind. Similar decisions have been made in Washington State, Montana, Colorado, California, the District of Columbia, and Vermont. At the time of publication, physician aid in dying is illegal in the 44 other states, and euthanasia continues to be illegal throughout the United States.

Regardless of personal positions on physician aid in dying and euthanasia, physicians are obligated to address the underlying concerns that lead patients and physicians to believe that physician aid in dying and euthanasia are necessary. Physicians should be acquainted with appropriate means of pain management and palliative care and treat a patient's distressing symptoms.

31

Men's Health[a]

THOMAS J. BECKMAN, MD

Benign Prostatic Hyperplasia

Benign prostatic hyperplasia (BPH) is common among older men. The prostate is the size of a walnut (20 cm^3) in men younger than 30 years and gradually increases in size, leading to BPH in most men older than 60 years. BPH results from epithelial and stromal cell growth in the prostate, which in turn causes urinary outflow resistance. Over time, this resistance leads to detrusor muscle dysfunction, urinary retention, and lower urinary tract symptoms (LUTS), such as urgency, frequency, and nocturia. Evidence has shown that BPH progresses when left untreated. This progression is manifested as worsened prostate symptom scores (see the History and Physical Examination section), decreased urinary flow rates, and increased risk of acute urinary retention. Other complications of BPH include urinary tract infections, obstructive nephropathy, and recurrent hematuria.

The diagnosis of BPH is challenging because prostate size correlates poorly with LUTS, and numerous conditions other than BPH cause LUTS (Table 31.1). Nonetheless, assessment of symptom severity, identification of prostatic enlargement on digital rectal examination (DRE), and documentation of decreased urinary flow rates with increased postvoid residual volumes yield accurate diagnoses in most cases.

Key Definition

***Benign prostatic hyperplasia**: urinary outflow resistance that results from epithelial and stromal cell growth in the prostate.*

History and Physical Examination

When obtaining a history of a man with suspected BPH, a clinician needs to consider the patient's age. Because prostate size increases with age, LUTS are most likely caused by BPH in men older than 50 years and most likely by other conditions in men younger than 40 years. A review of medications is also essential because many medications cause LUTS through their effect on the detrusor muscle and urinary sphincter function. Anticholinergic and antimuscarinic medications decrease detrusor muscle tone, sympathomimetic medications increase urethral sphincter tone, and diuretics increase urinary frequency (Table 31.1). Additionally, over-the-counter cold medications may cause LUTS through various mechanisms. When older men with subclinical BPH simply discontinue taking newly prescribed medications, LUTS often resolve. Finally, a focused review of systems should identify fever, hematuria (indicative of urothelial malignancy), urethral instrumentation or sexually transmitted diseases (suggestive of urethral stricture), sleep disturbances, patterns of fluid intake, and use of alcohol and caffeine.

The American Urological Association International Prostate Symptom Score (AUA/IPSS) is an objective measure of LUTS associated with BPH. The AUA/IPSS, which includes a questionnaire, aids in the BPH diagnosis and in follow-up of BPH progression over time (Figure 31.1). Numerous studies have shown its reliability and validity. The AUA/IPSS questionnaire asks about the following 7 urinary characteristics: frequency, nocturia, weak stream, hesitancy, intermittency, incomplete bladder emptying, and urgency. Each question is answered on a 5-point scale. When the response points to the 7 questions are summed, a score of 0 to 7 represents mild symptoms of BPH; 8 to 19, moderate symptoms; and 20 to 35, severe symptoms.

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[a] Portions previously published in Beckman TJ, Mynderse LA. Evaluation and medical management of benign prostatic hyperplasia. Mayo Clin Proc. 2005 Oct;80(10):1356-62. Errata in: Mayo Clin Proc. 2005 Nov;80(11):1533; and Beckman TJ, Abu-Lebdeh HS, Mynderse LA. Evaluation and medical management of erectile dysfunction. Mayo Clin Proc. 2006 Mar;81(3):385-90; used with permission of Mayo Foundation for Medical Education and Research

Table 31.1 • Differential Diagnosis for LUTS

Category	Examples	Comments
Malignant	Adenocarcinoma of the prostate Transitional cell carcinoma of the bladder Squamous cell carcinoma of the penis	Men should be offered PSA testing in conjunction with DRE With microhematuria on urinalysis, urothelial malignancy should be considered
Infectious	Cystitis Prostatitis Sexually transmitted diseases (eg, chlamydial infection, gonorrhea)	Urinalysis and urinary Gram stain are useful in evaluation for cystitis Prostatic massage specimens (VB3) assist in diagnosis of prostatitis Sexually transmitted diseases may cause LUTS from urethral scarring and stricture
Neurologic	Spinal cord injury Cauda equina syndrome Stroke Parkinsonism Diabetic autonomic neuropathy Multiple sclerosis Alzheimer disease	Primary mechanisms for neurologic causes of LUTS are detrusor weakness or uninhibited detrusor contractions (or both) Alzheimer disease can cause functional urinary incontinence
Medical	Poorly controlled diabetes mellitus Diabetes insipidus Congestive heart failure Hypercalcemia Obstructive sleep apnea	Medical conditions associated with urinary frequency are often overlooked causes of LUTS
Iatrogenic	Prostatectomy Cystectomy Traumatic urethrocystoscopic procedures Radiation cystitis	Surgical procedures sometimes cause neurologic impairment Traumatic urethrocystoscopic procedures can cause scarring and urethral strictures
Anatomical	BPH Ureteral and bladder stones	Hematuria may be seen on urinalysis Urinary cytologic, cystoscopic, and renal imaging studies should be considered
Behavioral	Polydipsia Excessive alcohol or caffeine consumption	Assessment of serum sodium level should be considered A voiding diary may provide useful information about fluid intake
Pharmacologic	Diuretics (eg, furosemide, hydrochlorothiazide) Sympathomimetics (eg, ephedrine, dextroamphetamine) Anticholinergics (eg, oxybutynin, amantadine) Antimuscarinics (eg, diphenhydramine, amitriptyline) Over-the-counter decongestants	Diuretics increase urinary frequency Sympathomimetic medications increase urethral resistance Anticholinergic and antimuscarinic medications decrease detrusor contractility Over-the-counter medications may cause LUTS through various mechanisms
Other	Overactive bladder	UDS can help distinguish BPH from isolated detrusor dysfunction

Abbreviations: BPH, benign prostatic hyperplasia; DRE, digital rectal examination; LUTS, lower urinary tract symptoms; PSA, prostate-specific antigen; UDS, urodynamic studies; VB3, voiding bottle 3 (postprostatic massage) urine specimen.

Modified from Beckman TJ, Mynderse LA. Evaluation and medical management of benign prostatic hyperplasia. Mayo Clin Proc. 2005 Oct;80(10):1356-62. Erratum in: Mayo Clin Proc. 2005 Nov;80(11):1533; used with permission of Mayo Foundation for Medical Education and Research.

A patient with LUTS should be evaluated for neurologic deficits, especially when the patient has a history of or presents with symptoms suggestive of a neurologic disorder. In such a case, useful findings include saddle anesthesia, decreased rectal sphincter tone, absent cremasteric reflex, or lower-extremity neurologic abnormalities. On examination of the abdomen, masses may be detected that result from a renal tumor, hydronephrosis, or bladder distention. The penis should be examined for pathologic changes. DRE findings most consistent with BPH are symmetrical enlargement and firm consistency, often likened to the thenar muscle or the tip of the nose. In contrast, findings consistent with adenocarcinoma of the prostate are prostate asymmetry, induration, and nodularity, often likened to the consistency of a knuckle or the forehead.

Evaluation

A specimen for urinalysis should be obtained routinely in the evaluation of men who have LUTS. Urinalysis findings of pyuria and bacteriuria suggest infection. Hematuria suggests

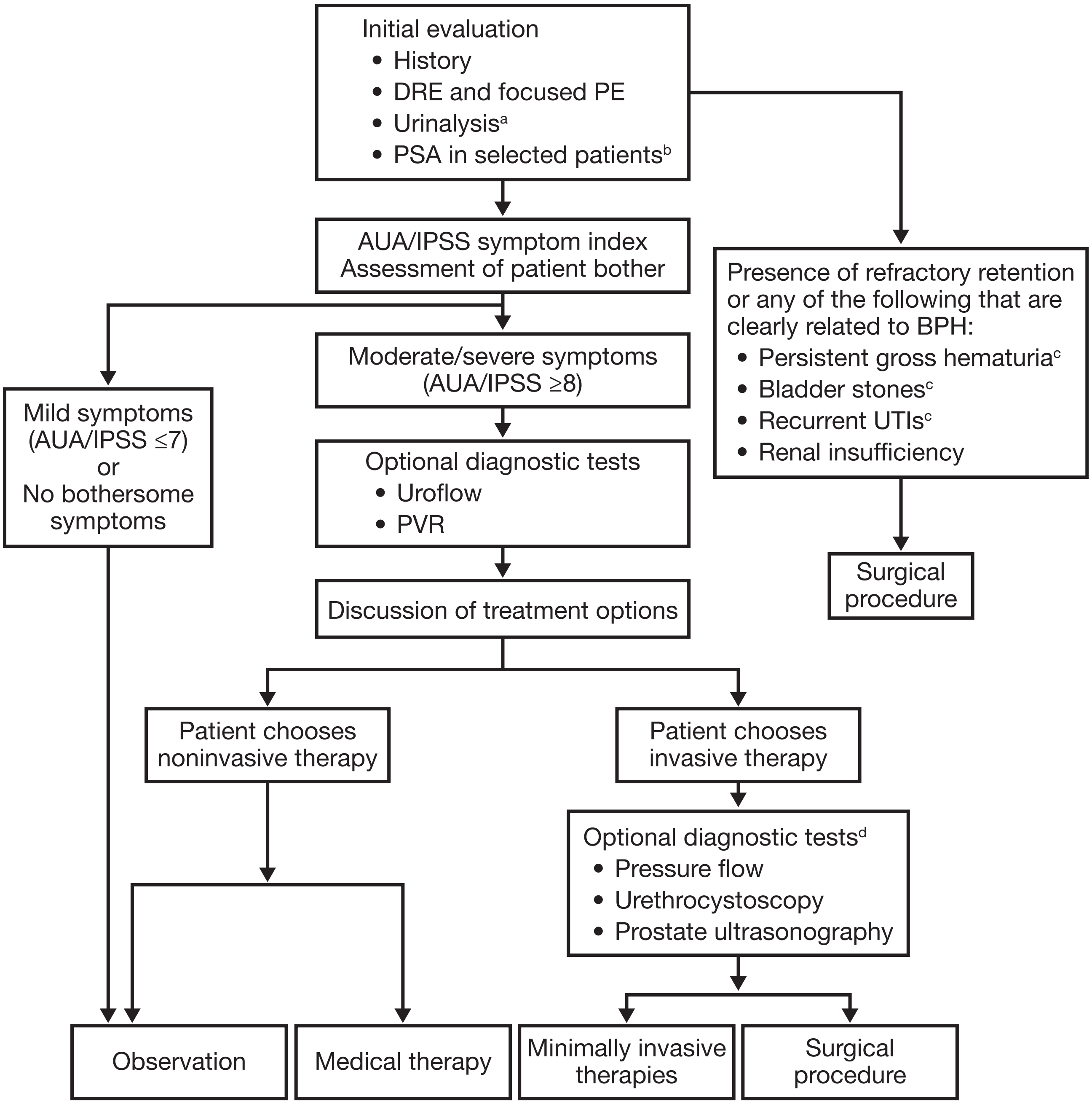
Initial evaluation
• History
• DRE and focused PE
• Urinalysis[a]
• PSA in selected patients[b]
AUA/IPSS symptom index
Assessment of patient bother
Presence of refractory retention or any of the following that are clearly related to BPH:
• Persistent gross hematuria[c]
• Bladder stones[c]
• Recurrent UTIs[c]
• Renal insufficiency
Surgical procedure
Mild symptoms (AUA/IPSS ≤7) or No bothersome symptoms
Moderate/severe symptoms (AUA/IPSS ≥8)
Optional diagnostic tests
• Uroflow
• PVR
Discussion of treatment options
Patient chooses noninvasive therapy
Patient chooses invasive therapy
Optional diagnostic tests[d]
• Pressure flow
• Urethrocystoscopy
• Prostate ultrasonography
Observation
Medical therapy
Minimally invasive therapies
Surgical procedure

Figure 31.1. *A Treatment Algorithm for Benign Prostatic Hyperplasia (BPH). Treatment decisions are based partly on patient symptom severity as determined with the American Urological Association International Prostate Symptom Score (AUA/IPSS). DRE indicates digital rectal examination; PE, physical examination; PSA, prostate-specific antigen; PVR, postvoid residual urine; UTI, urinary tract infection.* [a] *In patients with clinically significant prostatic bleeding, a course of a 5α-reductase inhibitor may be used. If bleeding persists, tissue ablative surgery is indicated.* [b] *Patients with at least a 10-year life expectancy for whom knowledge of the presence of prostate cancer would change management of BPH or patients for whom the PSA measurement may change the management of voiding symptoms.* [c] *After exhausting other therapeutic options.* [d] *Some diagnostic tests are used to predict response to therapy. Pressure-flow studies are most useful for men before surgical procedure.*

(Modified from AUA Practice Guidelines Committee. AUA guideline on management of benign prostatic hyperplasia [2003]. Chapter 1. Diagnosis and treatment recommendations. J Urol. 2003 Aug;170[2 Pt 1]:530-47; used with permission.)

Box 31.1 • Methods for Interpretation of Serum PSA Levels

Cutoff value. The traditional cutoff is 4 ng/mL

Age-adjusted values. Age-adjusted normal limits are commonly used because prostate volume increases with age

Ratio of free PSA to total PSA. The level of free (unbound) PSA is lower in men with adenocarcinoma of the prostate; therefore, a low ratio of free PSA to total PSA is more consistent with prostate adenocarcinoma than with BPH

PSA change velocity. A rapidly increasing PSA value is more suggestive of carcinoma than BPH; in particular, an annual PSA velocity greater than 0.75 ng/mL is considered abnormal

Abbreviations: BPH, benign prostatic hyperplasia; PSA, prostate-specific antigen.

inflammation or urothelial malignancy; active urine sediment suggests a possible postobstructive nephropathy.

Optional studies include measurement of serum creatinine and prostate-specific antigen (PSA). PSA measurement is optional because the results do not help discriminate BPH from adenocarcinoma of the prostate. Nevertheless, because LUTS may indicate prostate cancer, it is appropriate to routinely offer PSA testing. Evidence is conflicting about the utility of screening for prostate cancer with PSA. Yet, screening for prostate cancer with DRE and PSA may be appropriate for men age 50 to 75 years, depending on a patient's preference after a discussion in shared decision making with his physician. Methods for interpretation of serum PSA levels are listed in Box 31.1.

A uroflow study with ultrasonographic measurement of residual urine volume is an objective, noninvasive way to evaluate men presenting with LUTS. An accurate study requires urine volumes of at least 150 mL. Men with BPH often have peak flow rates less than 15 mL/s and increased residual urine volume (Figure 31.2). Of note, men with detrusor dysfunction also have abnormal results. Consequently, interpretation of the results of uroflow studies depends on the pretest probability of disease. If the pretest probability of BPH is high, an abnormal test result is useful for confirmation of the diagnosis. But if the pretest probability is intermediate, an abnormal uroflow result is less useful. In such cases, the patient may need to undergo complete urodynamic studies to further distinguish BPH from other causes of LUTS.

Medical Management of BPH

Clinicians should recognize the indications for urologic referral and invasive therapy. The indications are moderate or severe symptoms, persistent gross hematuria, urinary retention, renal insufficiency due to BPH, recurrent urinary tract infections, and bladder calculi.

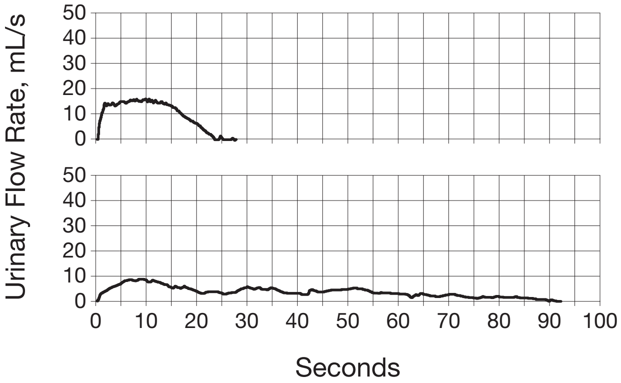

Figure 31.2. *Uroflow Tracings. Top graph, Uroflow tracing from a young, asymptomatic man. Of note, the parabolic flow curve and peak flow rate are greater than 15 mL/s. Bottom graph, Uroflow tracing from an elderly man with benign prostatic hyperplasia. Of note, the prolonged voiding time and peak flow rate are less than 10 mL/s. This patient's ultrasonographically measured residual urine volume was 100 mL.*

(Modified from Beckman TJ, Mynderse LA. Evaluation and medical management of benign prostatic hyperplasia. Mayo Clin Proc. 2005 Oct;80[10]:1356-62. Erratum in: Mayo Clin Proc. 2005 Nov;80[11]:1533; used with permission of Mayo Foundation for Medical Education and Research.)

Observation is reasonable for patients with mild or moderate symptoms. These patients are monitored yearly or when new symptoms arise. In addition, these patients may be advised to practice scheduled voiding (every 3 hours during the day), avoid excess evening fluid intake, and be aware of adverse effects of over-the-counter decongestants.

Most patients presenting with BPH are candidates for medical therapy, which has replaced interventional therapy as the most common BPH treatment. Prescription medications available for BPH are α_1-adrenergic antagonists (eg, tamsulosin), 5α-reductase inhibitors (eg, finasteride), and phosphodiesterase type 5 inhibitors (eg, tadalafil).

The α_1-adrenergic antagonist medications, the first line of therapy, work on the dynamic component of bladder outlet obstruction by decreasing prostatic smooth muscle tone. Although all α_1-adrenergic antagonist medications are equally efficacious, terazosin and doxazosin are more likely to cause orthostatic hypotension than other medications in this class. Other adverse effects include dizziness, hypotension, edema, palpitations, **erectile dysfunction** (ED), and fatigue.

The second class of prescription medications for BPH, the 5α-reductase inhibitors, act on the static (anatomical) component of bladder outlet obstruction. They decrease the conversion of testosterone to dihydrotestosterone in the prostate, thereby limiting prostate growth. Commonly prescribed 5α-reductase inhibitors are finasteride and dutasteride.

The following points about finasteride are noteworthy. It is most useful for severe BPH and large prostate (>40 cm^3). Finasteride may need to be taken for more than 6 months to observe optimal effects, and it can decrease serum PSA level substantially. Therefore, experts recommend correction of serum PSA for men taking finasteride by multiplying the PSA value by 2. Adverse effects with finasteride are uncommon and usually related to sexual dysfunction, including decreased libido, ejaculatory dysfunction, and ED. Finally, evidence supports combination therapy with α_1-adrenergic antagonist and 5α-reductase inhibitor for men with inadequate responses to either drug alone.

Herbal medications used to treat BPH include African star grass, African plum tree bark, rye grass pollens, stinging nettle, and cactus flower. The most commonly used alternative treatment of BPH is saw palmetto (*Serenoa repens*). Saw palmetto is considered safe, and studies have shown that compared with placebo, saw palmetto improves flow and decreases symptoms.

KEY FACTS

- ✓ For men with BPH, prostate size on examination correlates poorly with LUTS
- ✓ For men presenting with LUTS, the test that should always be considered is urinalysis with microscopy
- ✓ Men with BPH should be referred to a urologist for possible invasive therapy if they have moderate or severe symptoms, persistent gross hematuria, urinary retention, renal insufficiency due to BPH, recurrent urinary tract infections, or bladder calculi
- ✓ Nearly all men with BPH are candidates for medical therapy—α_1-adrenergic antagonist medications are considered first-line therapy

Erectile Dysfunction

Male sexual dysfunction includes ED, decreased sexual desire (libido), anatomical abnormalities (eg, Peyronie disease), and ejaculatory dysfunction. ED, sometimes defined as the inability to achieve erections firm enough for penetration, affects millions of men in the United States. The Massachusetts Male Aging Study showed that the prevalence of ED increased with age: Approximately 50% of men had ED at age 50 years and nearly 70% at age 70.

Key Definition

Erectile dysfunction: *the inability to achieve erections firm enough for penetration.*

KEY FACTS

- ✓ Risk factors for ED and cardiovascular disease are nearly identical; risk of ED is lower for men who are physically active and have normal body mass index
- ✓ Patients should be instructed to take PDE-5 inhibitors on an empty stomach at least 1 hour before sexual activity
- ✓ Men who can achieve tasks of 5 to 6 metabolic equivalents on cardiac stress testing without evidence of ischemia likely can safely engage in sexual activity and take PDE-5 inhibitors
- ✓ Testosterone replacement has not been shown to improve erectile function for men with normal serum testosterone levels

Erectile physiologic factors include hormonal, vascular, psychological, neurologic, and cellular components. Testosterone is primarily responsible for maintenance of libido and hypogonadism is sometimes associated with ED. Other hormonal causes of ED include hyperthyroidism and prolactinomas. The penile blood supply begins at the internal pudendal artery, which branches into the penile artery, ultimately branching to the cavernous, dorsal, and bulbourethral arteries. Psychogenic erections, triggered by fantasy or visual stimulation, are mediated by sympathetic input from the thoracolumbar chain (T11 through L2). Reflex erections are caused by tactile stimulation and are mediated by the parasympathetic nervous system (S2 through S4). Overall, parasympathetic signals are responsible for erection, and sympathetic signals are responsible for ejaculation.

Sexual arousal and parasympathetic signals to the penis initiate intracellular changes necessary for erection (Figure 31.3). Endothelial cells release nitric oxide, which in turn increases the level of cyclic guanosine monophosphate (cGMP). Increased cGMP levels cause relaxation of arterial and cavernosal smooth muscle and increased penile blood flow. As intracavernosal pressure increases, penile emissary veins are compressed, thus restricting venous return from the penis. The combination of increased arterial flow and decreased venous return results in erection. This process is reversed by the activity of cGMP phosphodiesterase (PDE) type 5 (PDE-5), which breaks down cGMP, resulting in erection cessation.

Although ED is generally not an indicator of serious diseases, it is strongly associated with cardiovascular risk factors. In fact, the Health Professionals Follow-up Study showed that risk factors for ED and cardiovascular disease were nearly identical and that physically active men had a 30% lower risk of ED than inactive men. Therefore, men with diabetes mellitus, hypertension, and coronary artery disease are at increased risk for ED. Not surprisingly, randomized controlled trial data show that erectile function substantially improves in obese men who lose weight through diet and exercise.

Evaluation of Patients Who Have ED

History and Physical Examination

Certain questions should be asked routinely when taking a history from patients who have ED (Table 31.2). Especially important are questions about the common ED risk factors: cardiovascular disease, smoking, diabetes mellitus, hypertension, hyperlipidemia, prescription medications, alcohol use, recreational drug use, and mood disorders. In addition, validated questionnaires, such as the International Index of Erectile Function, are useful for monitoring a patient's response to ED treatment.

A complete multisystem examination may identify indicators of cardiovascular disease (eg, obesity, hypertension, femoral arterial bruits), endocrinopathy (eg, visual field defects, thyromegaly, gynecomastia), or neurologic abnormalities (eg, decreased sphincter tone, absent bulbocavernosus reflex, saddle anesthesia). The penis should be palpated in the stretched position to detect fibrous plaques consistent with Peyronie disease, which may be present on the dorsum and base of the penis. The testicles should be evaluated for masses (indicative of malignancy) and decreased size and soft consistency (indicative of hypogonadism). Finally, the examination of a patient with ED is often a good opportunity to screen for prostate cancer and to assess for benign glandular enlargement.

Laboratory Testing

Although disease-specific testing is favored, serum testosterone levels are often measured in a men's health practice. If a patient has a hypogonadal condition, serum prolactin and luteinizing hormone levels should be assessed. If the prolactin level is elevated or the luteinizing hormone level is not elevated, magnetic resonance imaging of the brain should be used to rule out a pituitary adenoma. Additional useful tests that pertain to ED risk factors include measurement of fasting glucose, fasting lipids, and thyrotropin.

Medical Management of ED

PDE-5 Inhibitors

The PDE-5 inhibitor medications are the first line of therapy for most men with ED. PDE-5 inhibitors have revolutionized the treatment of ED since the introduction of sildenafil in 1998, and experts have observed that these medications have considerably affected (both positively and negatively) the sexual culture of older people. There were initial concerns about cardiovascular risks associated with PDE-5 inhibitors, but studies have shown that these medications are generally safe, even for patients with stable coronary artery disease who are not taking nitrate therapy.

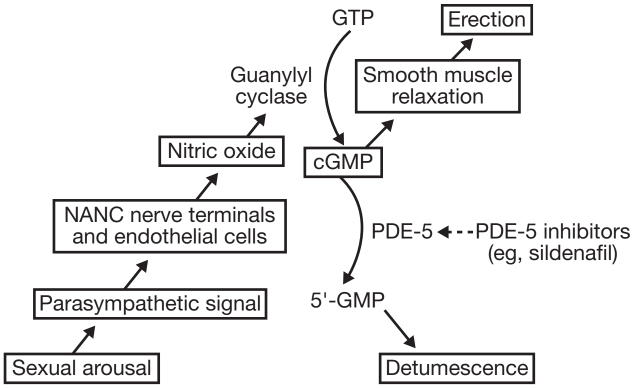

Figure 31.3. Mechanism for Penile Erection and the Molecular Activity of Phosphodiesterase Type 5 (PDE-5) Inhibitor Medications. cGMP indicates cyclic guanosine monophosphate; GMP, guanosine monophosphate; GTP, guanosine triphosphate; NANC, nonadrenergic noncholinergic.

(Modified from Beckman TJ, Abu-Lebdeh HS, Mynderse LA. Evaluation and medical management of erectile dysfunction. Mayo Clin Proc. 2006 Mar;81[3]:385-90; used with permission of Mayo Foundation for Medical Education and Research.)

Three commonly prescribed PDE-5 inhibitor medications are sildenafil, vardenafil, and tadalafil. Sildenafil is also available as a generic prescription. These medications inhibit cGMP PDE-5, thereby increasing cGMP levels and shifting the physiologic balance in favor of erection (Figure 31.3). In the absence of comparative clinical trials and meta-analyses, these medications appear to be equally efficacious. Tadalafil has a longer half-life (up to 36 hours) than sildenafil or vardenafil, which affords more spontaneity. Patients should be instructed to take PDE-5 inhibitors at least 1 hour before sexual activity and on an empty stomach. Patients should also realize that PDE-5 inhibitors will not cause erections in the absence of sexual arousal (unlike intraurethral alprostadil and penile injection therapy).

The PDE-5 inhibitors have several common adverse effects due to the presence of PDE throughout the body: headache, flushing, gastric upset, diarrhea, nasal congestion, and lightheadedness. A distinctive reaction to sildenafil is blue-tinged vision, which is probably related to the activity of sildenafil on PDE type 6 (PDE-6) in the retina. This reaction resolves with discontinuation of therapy. Of note, some varieties of retinitis pigmentosa involve a PDE-6 gene defect. Consequently, patients with retinitis pigmentosa should not receive medications from the PDE-5 inhibitor class.

A contraindication to the use of PDE-5 inhibitors is nitrate therapy. Indeed, patients treated for acute coronary syndromes should not receive nitrate therapy within 24 hours of taking sildenafil or vardenafil and within 48 hours of taking tadalafil. Physicians should also be cautious about prescribing PDE-5

Table 31.2 • Questions to Ask When Taking a History From a Patients With ED

Question	Comment
Do you have difficulty achieving erections or difficulty with orgasms and ejaculation?	Sexual dysfunction includes various diagnoses, so it is important to determine whether the patient's primary concern is ED
How often do you achieve erections? Are your erections firm enough for penetration?	Often patients are not satisfied with the quality of their erections, yet if patients can achieve erections adequately firm for penetration most of the time, their concerns are not classically defined as ED
Did your ED occur suddenly? Do you have nocturnal erections? Do you feel anxious or depressed? Do you and your partner have a satisfactory relationship?	The sudden onset of ED and the persistence of nocturnal erections indicate an inorganic (psychogenic) cause; in such cases, the physician should explore the psychosocial context of the patient's sexual history, such as whether the patient feels anxious or depressed or whether the patient has interpersonal relationship difficulties
Do you have a desire to engage in sexual activity?	Decreased sexual desire may indicate hypogonadism; if the patient is not interested in sexual activity, serum testosterone levels should be assessed and mood disorders should be considered
Do you have penile curvature or pain with erections?	A positive response to this question may indicate Peyronie disease, which is sometimes detected on physical examination; identification of Peyronie disease is important because it precludes intraurethral alprostadil and penile injection therapy
Can you engage in vigorous physical activity without chest pain or unusual dyspnea?	PDE-5 inhibitor medications will be considered for most patients, and sexual activity is associated with cardiovascular stress; hence, a history should be obtained to identify undiagnosed ischemic heart disease or to assess the stability of known ischemic heart disease
What medications are you taking?	Numerous medications are associated with ED, especially antihypertensives and psychotropics; medications that inhibit cytochrome P-450 (eg, ritonavir) should be identified because they increase plasma levels of PDE-5 inhibitor medications; an absolute contraindication to PDE-5 inhibitors is the concurrent use of nitrates (eg, isosorbide mononitrate); a combination of PDE-5 inhibitors and α_1-adrenergic antagonists can cause hypotension
How much alcohol do you consume? Do you use illegal drugs?	Substance abuse, including alcoholism, is commonly overlooked as a cause of ED
Which ED treatments have you already tried?	Knowledge of which medications the patient has tried will help the physician decide the next therapeutic plan
Do you have a history of diseases involving your heart, blood vessels, nervous system, or hormones?	Common risk factors for ED should be identified
Do you have a history of hypertension, hyperlipidemia, diabetes mellitus, or tobacco abuse?	
Do you have a history of penile trauma or genitourinary surgery?	
Do you ride a bicycle regularly?	Prolonged, frequent bicycle riding can cause excessive pudendal pressure, leading to ED

Abbreviations: ED, erectile dysfunction; PDE-5, phosphodiesterase type 5.

Modified from Beckman TJ, Abu-Lebdeh HS, Mynderse LA. Evaluation and medical management of erectile dysfunction. Mayo Clin Proc. 2006 Mar;81(3):385-90; used with permission of Mayo Foundation for Medical Education and Research.

inhibitors for patients with poorly controlled blood pressure or multidrug antihypertensive regimens. In patients with known or suspected ischemic heart disease, cardiac stress testing is useful for stratifying the risk of PDE-5 inhibitor therapy. Patients who achieve tasks of 5 to 6 metabolic equivalents without ischemia probably have a low risk of complications from engagement in sexual activity.

Treatment options for patients who have not had a response to PDE-5 inhibitors or who cannot take PDE-5 inhibitors include intraurethral alprostadil and penile injection therapy. These agents are generally more effective than PDE-5 inhibitors, but their obvious drawback is inconvenience. Contraindications for these treatments include blood cell dyscrasias (eg, sickle cell disease, leukemia, multiple myeloma) and penile deformity, especially Peyronie disease. Anticoagulation is an additional contraindication to penile injection therapy. Information is inadequate on the safety of PDE-5 inhibitors used in combination with injection therapy, and hence, their coadministration is not advised.

Intraurethral Alprostadil

Intraurethral alprostadil is effective for men of all ages who have ED from various causes. Intraurethral alprostadil is inserted with an applicator into the urethral meatus at the tip of the penis. Patients should be instructed on the application technique. Additionally, owing to the risk of syncope, administration of the first dose should be supervised by a health care provider. The most common adverse effect is urethral and genital burning, and hypotension can occur. As for all medical ED treatments, patients are educated about priapism and are instructed to go to an emergency department if they have erections for more than 4 hours.

Intracavernosal Penile Injections

Intracavernosal penile injection, an efficacious and generally safe therapy, is the most effective medical treatment of ED. In practice, a triple-therapy combination of alprostadil, papaverine, and phentolamine is often used. These medications increase penile blood flow. Specifically, alprostadil and papaverine cause relaxation of cavernosal smooth muscle and penile blood vessels, and phentolamine antagonizes α-adrenoreceptors. Although many patients are hesitant to attempt penile injection, this method is associated with minimal discomfort.

Testosterone

Various hormonal therapies, including testosterone, were once widely used to treat ED. The penile nitric oxide pathway is testosterone dependent; therefore, screening for low serum testosterone levels is necessary for men who have no response to medical therapy with sildenafil or whose presentation suggests hypogonadism. Hypogonadism is diagnosed from the presence of hypogonadal symptoms (eg, decreased libido, cognitive decline, generalized muscle weakness) and from morning fasting total testosterone levels less than 200 ng/dL on at least 2 separate occasions. Among men with hypogonadism, PDE-5 inhibitor therapy in combination with testosterone is often effective. Testosterone replacement alone increases sexual interest, nocturnal erections, and frequency of sexual intercourse. Nevertheless, testosterone replacement has not been shown to improve erectile function of men with normal serum testosterone levels.

Testosterone is available by injection, skin patch, topical gel, or buccal oral tablets. Testosterone therapy is associated with potential risks. For example, prolonged use of high-dose, orally active 17α-alkyl androgens (eg, methyltestosterone) is associated with hepatic neoplasms, fulminant hepatitis, and cholestatic jaundice. Other risks of exogenous testosterone therapy include gynecomastia, alterations in the lipid profile (mainly decreased high-density lipoprotein cholesterol), erythropoietin-mediated polycythemia, edema, sleep apnea, hypertension, infertility (through suppression of spermatogenesis), and BPH. Exogenous testosterone also increases the risk of prostate carcinoma. Although testosterone replacement may not cause prostate carcinoma, it could stimulate the growth of existing occult prostate cancer. For this reason, all men should have screening for prostate cancer with DRE and serum PSA before using exogenous testosterone.

The goal of testosterone replacement is to increase serum testosterone levels to the low or middle portion of the reference range. A recommended treatment is topical testosterone 1% gel at a starting dose of 50 g daily, applied to the shoulders, upper parts of the arms, or abdomen. A total testosterone level may be reassessed as soon as 14 days after starting treatment. The patient's therapeutic response and testosterone level are reassessed at 3 months, and decisions are then made about whether to continue testosterone use and whether to adjust the dose.

Patients who have serum testosterone levels in the normal range as a result of testosterone replacement therapy should not be at risk for adverse effects. However, the monitoring of patients during testosterone therapy is essential. Baseline determinations include whether the patient has a history of prostate cancer, BPH, obstructive sleep apnea, liver disease, hypertension, or hyperlipidemia. Baseline testing includes a complete blood cell count and levels of serum PSA, lipids, and liver transaminases. PSA levels and prostate-related symptoms should be assessed at 6 months and then annually, and patients with elevated or increasing PSA levels should not receive testosterone treatment. Hematocrit and lipid levels should be monitored semiannually for the first 18 months and annually thereafter. The testosterone dose should be decreased or therapy discontinued if hematocrit values are greater than 50%. Finally, patient response to therapy and adverse effects should be monitored quarterly during the first year of treatment.

Nonmedical Treatments

Other ED treatments include topical vacuum pump devices and surgically inserted inflatable penile implants. Penile pumps work by creating a vacuum around the penis, thus drawing blood into the penis. When the penis is engorged with blood, an elastic ring is placed over the base of the penis and the pump is removed. Importantly, patients should use vacuum pump devices with vacuum limiters, which prevent negative pressure injury to the penis. Penile implants are generally not offered unless a patient has no response to medical treatments, including maximal-strength injection therapy.

32 Otolaryngology and Ophthalmology

NERISSA M. COLLINS, MD

Otolaryngology

Otitis Externa

Acute Otitis Externa

Acute otitis externa, also known as *swimmer's ear*, is an infection of the external auditory canal. A moist environment, eczematous dermatitis, repeated insertion of foreign bodies (eg, cotton swabs), and psoriasis can predispose to otitis externa. Most patients present with otalgia and otorrhea. On examination, the tympanic membrane appears normal, but the external auditory canal is erythematous, often with exudate. Typical examination findings include pain with pressure on the tragus and with traction of the pinna. Management of otitis externa includes avoidance of excessive water exposure and application of topical antibiotics and topical corticosteroids.

Malignant Otitis Externa

Malignant otitis externa is a feared complication of acute otitis externa in patients with diabetes mellitus and with other immunocompromise. It typically is caused by *Pseudomonas aeruginosa*. The infection can penetrate the cartilaginous structures of the ear canal and extend into the temporal bone, where it causes osteomyelitis. Patients present with severe pain, fever, and possibly cranial neuropathies. On examination, granulation tissue is often present in the external auditory canal. The condition requires emergent care with intravenous antibiotics and sometimes surgical débridement of the skull base osteomyelitis.

Pharyngitis

Most cases of pharyngitis are viral. The goal is to identify the patients with group A streptococcal (GAS) pharyngitis and to treat them to prevent rheumatic fever. In the Centor clinical prediction criteria for the diagnosis of GAS pharyngitis, 1 point is assigned for each of the following: fever, anterior cervical lymphadenopathy, tonsillar exudates, and absence of cough.

The modified Centor criteria adds a point if the patient is younger than 18 years and subtracts a point if the patient is older than 44 years. Patients who have no more than 1 Centor criterion have a low probability of GAS pharyngitis and should be observed. Most guidelines suggest rapid streptococcal antigen testing; only when test results are positive and the patient has 2 or 3 criteria should treatment with antibiotics be initiated. If all 4 criteria are present, empirical antibiotic therapy is indicated. Recommended first-line agents include penicillin and amoxicillin for 10 days. For patients with a nonanaphylactic allergy to penicillin, the clinician can use a first-generation cephalosporin for 10 days, clindamycin or clarithromycin for 10 days, or azithromycin for 5 days.

Ophthalmology

Red Eye

The red eye is a common ocular concern. Although most causes are benign, the clinician should be able to recognize the syndromes on examination and determine when an emergent referral to an ophthalmologist is indicated.

Subconjunctival Hemorrhage

Subconjunctival hemorrhage (Figure 32.1) is typically unilateral and painless. It may follow trauma, coughing, straining, or emesis. Subconjunctival bleeding also occurs when patients have uncontrolled arterial hypertension, treatment with anticoagulants or antiplatelet agents, and intrinsic disorders of coagulation. It resolves spontaneously and requires only reassurance.

Conjunctivitis

Conjunctivitis can result from allergic, viral, and bacterial causes. Patients with allergic conjunctivitis present with bilateral

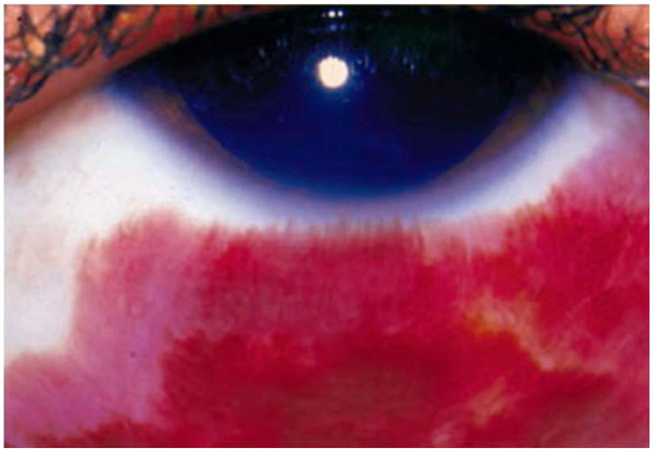

Figure 32.1. *Subconjunctival Hemorrhage. The sharply demarcated hemorrhage prevents visualization of underlying structures. No inflammation is observed in contiguous areas. This disorder does not affect vision and almost always clears spontaneously.*
(From Leibowitz HM. The red eye. N Engl J Med. 2000 Aug 3;343[5]:345-51; used with permission.)

red, itchy eyes and excessive tearing. Other allergic symptoms, such as sneezing and nasal congestion, typically accompany the eye symptoms. Systemic or topical antihistamines are usually effective for symptom management.

Viral conjunctivitis causes bilateral ocular redness, irritation, and excessive tearing. Preauricular lymphadenopathy may be present. Viral conjunctivitis is usually caused by an adenovirus and is highly contagious. It is a self-limited condition, and no antimicrobials are warranted.

Patients with bacterial conjunctivitis usually present with acute unilateral redness, irritation, and discharge. The infection warrants topical antibacterial therapy. A bacterial conjunctivitis that fails to resolve within 7 to 10 days should prompt consultation with an ophthalmologist. Chlamydial and gonorrheal conjunctivitis should be suspected in high-risk patients.

KEY FACTS

- ✓ Predisposing factors for otitis externa—moist environment, eczematous dermatitis, foreign bodies (eg, cotton swabs), psoriasis
- ✓ Malignant otitis externa—calls for emergent care with intravenous antibiotics and sometimes surgical débridement
- ✓ For GAS pharyngitis, penicillin and amoxicillin are the recommended first-line agents
- ✓ Usual presenting symptoms of bacterial conjunctivitis—acute unilateral redness, irritation, and discharge

Blepharitis

A **hordeolum,** or **stye**, is an infectious, painful, erythematous, localized nodule of the eyelid. An external hordeolum is caused by a blockage and subsequent infection of the glands of the eyelid. An internal hordeolum is caused by infection of the meibomian glands. *Staphylococcus aureus* is responsible for many of these infections. Although most of these lesions drain spontaneously, some require incision and drainage by an ophthalmologist. Application of warm compresses may assist in spontaneous drainage. Antibiotics are not generally required unless the infection has spread beyond the nodule.

Key Definition

Hordeolum, *or* **stye:** *an infectious, painful, erythematous, localized nodule of the eyelid.*

A chalazion is a chronic, rarely painful, and always internal noninfectious eyelid disorder. It is caused by granulomatous inflammation in the meibomian glands. A chalazion can be removed if it is bothersome or large.

Episcleritis

Patients with episcleritis (Figure 32.2) present with sectorial injection of the episcleral vessels. Most episcleritis cases are idiopathic, but sometimes a disease is associated. Typically, the diseases associated with it are the same as those associated with scleritis. The condition is usually self-limited, and an oral nonsteroidal anti-inflammatory medication is usually sufficient to relieve symptoms.

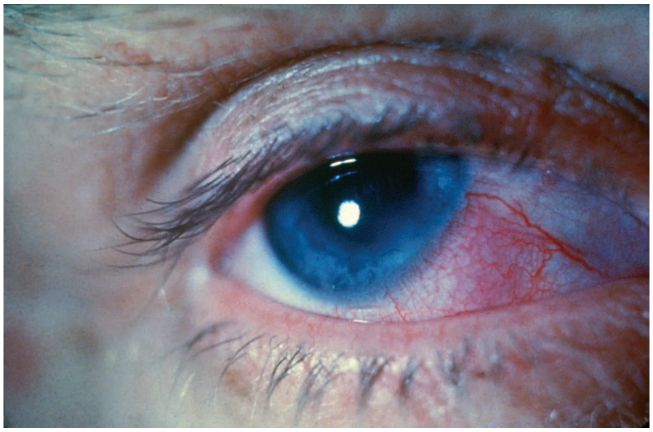

Figure 32.2. *Episcleritis. Segmental bright-red injection. Distinguished from conjunctivitis by the absence of discharge.*
(Modified from McDonald FS. Mayo Clinic images in internal medicine: self-assessment for board exam review. Rochester [MN]: Mayo Clinic Scientific Press and Boca Raton [FL]: CRC Press; c2004. p. 123; used with permission of Mayo Foundation for Medical Education and Research.)

Scleritis

Scleritis manifests as an intense, deep pain in the eye caused by scleral inflammation. The pain worsens with movement of the eye and may be referred to the ipsilateral temple. On examination, the scleral vessels are dilated and the eye appears red. Many patients with scleritis have an associated systemic disorder, such as polyarteritis nodosa, systemic lupus erythematosus, granulomatosis with polyangiitis, seronegative spondyloarthropathies (eg, ankylosing spondylitis), and rheumatoid arthritis. Successful therapy requires treatment with topical corticosteroids, topical cycloplegic agents, and systemic therapy for any underlying disease.

Iritis

Iritis, also called *acute anterior uveitis* (Figure 32.3), is inflammation of the iris and ciliary body. Patients typically present with erythema, photophobia, pain, and blurred vision. Disorders associated with iritis include autoimmune diseases. Patients with HLA-B27 are at increased risk for iritis. The diagnosis requires a slit-lamp examination, and immediate referral to an ophthalmologist is necessary.

Key Definition

Iritis: *inflammation of the iris and ciliary body. Also called* acute anterior uveitis.

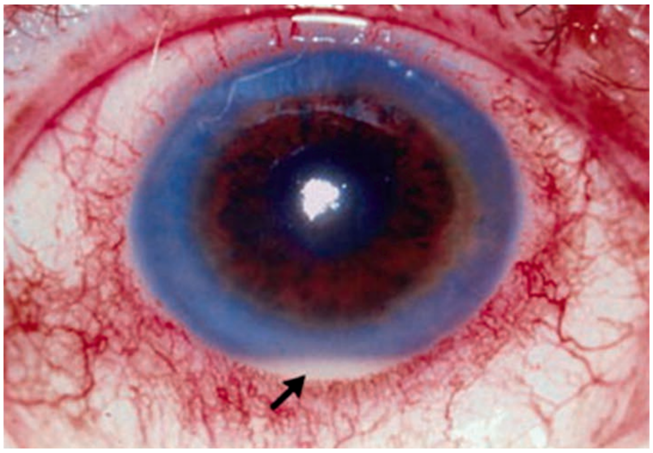

Figure 32.3. *Acute Anterior Uveitis. The pupil is constricted, is irregular, and reacts poorly to light. Conjunctival hyperemia is most pronounced adjacent to the limbus. A hypopyon is present (arrow). This disorder can cause vision loss and warrants immediate referral to an ophthalmologist.*

(From Leibowitz HM. The red eye. N Engl J Med. 2000 Aug 3;343[5]:345-51; used with permission.)

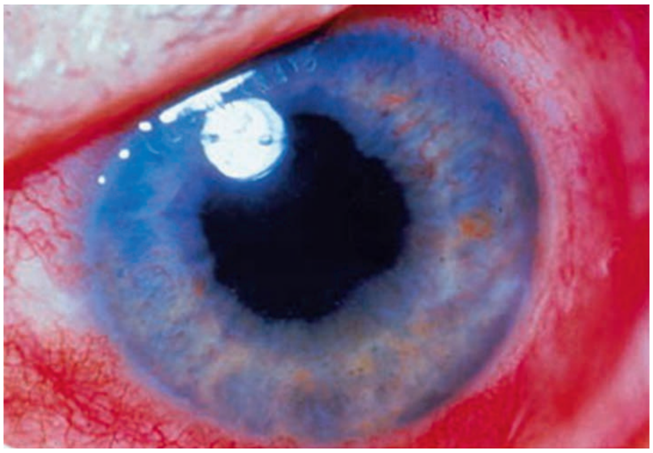

Figure 32.4. *Angle-Closure Glaucoma. The pupil is moderately dilated and unreactive to light. Corneal edema causes the iris markings to appear less sharp than those of the unaffected eye. Prompt, aggressive treatment of this disorder is necessary to prevent optic atrophy.*

(From Leibowitz HM. The red eye. N Engl J Med. 2000 Aug 3;343[5]:345-51; used with permission.)

Angle-Closure Glaucoma

The development of acute angle-closure glaucoma (Figure 32.4) is a medical emergency. Patients present with abrupt ocular pain, headache, decreased vision, and often nausea. Frequently, the eye has diffuse redness, a middilated pupil that reacts poorly to light, and corneal cloudiness. Risk factors for primary angle-closure glaucoma include a family history of the same, age greater than 60 years, female sex, hyperopia (farsightedness), Asian race and ethnicity, and pseudoexfoliation. Patients with acute angle-closure glaucoma should be emergently evaluated by an ophthalmologist.

Glaucoma

Glaucoma is a form of optic neuropathy caused by increased intraocular pressure. Risk factors for the open-angle glaucoma type include age, African American race and ethnicity, and diabetes mellitus. Most patients with glaucoma are treated with ocular hypotensive drops. Patients who cannot tolerate topical eye medications or those whose glaucoma progresses despite treatment are candidates for surgical therapy, such as laser trabeculoplasty.

Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a common cause of visual impairment in older adults. Women and cigarette smokers are at higher risk for AMD. The disease has 2 forms: dry and wet. Dry AMD is characterized by soft drusen and pigmentary changes, whereas wet AMD is characterized by exudative and choroidal neovascular changes. Patients with dry AMD typically present with gradually advancing symptoms that include loss of central vision, central scotoma, visual distortion, and color changes. In wet AMD, the changes often occur more abruptly.

Treatment options for AMD are limited. However, on the basis of the Age-Related Eye Disease Study trials, patients with dry or wet AMD should consider treatment with a dietary supplement containing vitamin C, vitamin E, lutein, zeaxanthin, zinc, and copper. In addition, certain patients with wet AMD may benefit from such specific therapies as intravitreous injection of vascular endothelial growth factor inhibitor, thermal laser photocoagulation, and photodynamic therapy.

KEY FACTS

✓ Scleritis—often associated with polyarteritis nodosa, systemic lupus erythematosus, granulomatosis with polyangiitis, seronegative spondyloarthropathies, and rheumatoid arthritis

✓ Acute angle-closure glaucoma is a medical emergency

✓ Risk factors for open-angle glaucoma—age, African American race and ethnicity, diabetes mellitus

✓ AMD is more likely in women and cigarette smokers

33 Palliative Care[a]

AMANDA K. LORENZ, MD; JACOB J. STRAND, MD; ELISE C. CAREY, MD

Pain Management for Patients With Serious Illness

Cancer-related pain affects up to 50% of patients receiving cancer-directed therapies and between 70% and 90% of patients with advanced-stage cancers. However, pain is a common symptom for many patients with serious illness other than cancer. Patients with chronic obstructive pulmonary disease, heart failure, end-stage renal disease requiring hemodialysis, and various neurodegenerative disorders experience pain from their conditions. In these cases, pain is often underrecognized and undertreated, which can lead to functional impairment and suboptimal quality of life.

Barriers to optimal pain management include inadequate pain assessment by health care professionals, clinician reluctance to prescribe opioids, inadequate knowledge about the safe use of opioid therapy, and public fear of opioid misuse. Palliative care and end-of-life care are specifically excluded from the 2016 Centers for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain. Yet, the current climate of opioid misuse for chronic pain, while beyond the scope of this chapter, influences all of the barriers mentioned above.

General Principles

For pain related to a serious illness, reversible causes should be sought and treated as indicated by the history, physical examination findings, results of pertinent imaging studies, and patient goals. Identification of the cause of a patient's pain can help the clinician tailor treatment appropriately. For most patients with pain due to a serious illness, such as cancer-related pain, a combination of opioid therapy and nonopioid therapy is required.

Oral medications continue to be the most common form of opioids used to treat cancer-related pain. The opioids commonly prescribed in clinical practice (eg, morphine, oxycodone, hydromorphone) are not systemically absorbed through the buccal mucosa in appreciable concentrations and thus take 30 to 60 minutes to reach peak effect. Lipophilic drugs, such as methadone, fentanyl, and ketamine, have better transmucosal (buccal or sublingual) absorption, but their use typically requires the input of a specialist in palliative care or anesthesia pain.

When rapid analgesia is required because of severe pain or the limitations of the oral route, parenteral medications should be used. Intravenous opioids reach peak effect in 5 to 15 minutes and subcutaneous opioids in 20 to 30 minutes. Intramuscular administration of opioids is strongly discouraged because of both pain from the injection and erratic drug absorption.

Patient Evaluation

Evaluation of a patient in pain should include 3 components. A detailed history should be taken regarding onset, quality, severity, timing, and location of pain; exacerbating and relieving factors; and associated symptoms. The patient should receive a comprehensive physical examination, including neurologic assessment. Diagnostic studies should be performed, guided by the history and physical examination findings. Of note, administration of analgesia should not be delayed while awaiting results of diagnostic studies or other tests.

Occasionally, the pain reported by a patient is poorly controlled despite escalating doses of appropriate medical therapy. This can sometimes be an indication that other stressors are contributing to the patient's experience of the pain. The concept that pain expression is a combination of physical, emotional,

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[a] Portions previously published in Mueller PS, Hook CC, Hayes DL. Ethical analysis of withdrawal of pacemaker or implantable cardioverter-defibrillator support at the end of life. Mayo Clin Proc. 2003 Aug;78(8):959-63; used with permission of Mayo Foundation for Medical Education and Research.

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psychosocial, and spiritual components is referred to as *total pain*. Further evaluation and referral to supportive services, such as physical therapy, social work, or chaplaincy, could be considered.

Pain Treatment

Treatment of pain for patients with life-threatening illness follows a 3-tiered approach, as outlined by the World Health Organization in the analgesic ladder for cancer-pain relief (Box 33.1). Mild pain may respond to nonopioid treatments if administration of these medications is clinically appropriate. Adjuvant therapies, such as anticonvulsants for neuropathic pain and corticosteroids and bisphosphonates for bone pain, should be added at any pain level if clinically indicated. Algorithms are available for treatment of severe cancer pain (pain score of 7-10 on a 0-to-10 scale) with intravenous opioids and moderate cancer pain (pain score of 4-6 on a 0-to-10 scale) with oral opioids (Figures 33.1 and 33.2).

Box 33.1 • Three-Tiered Ladder Approach to Cancer Pain Treatment, Suggested by the World Health Organization

- Step 1. Mild pain
  - Acetaminophen
  - Nonsteroidal anti-inflammatory drugs
  - Nonopioid adjuvants (eg, neuropathic agents, topical analgesics)
- Step 2. Moderate pain
  - Add a short-acting opioid to step 1 therapies
    - Oxycodone immediate release
    - Morphine immediate release
    - Hydromorphone
  - Avoid opioid-acetaminophen combinations (not recommended because of acetaminophen's dose limitations)
  - Avoid codeine products (not recommended because of variable pharmacokinetics and metabolism)
- Step 3. Severe pain
  - For severe pain or inadequate pain relief with steps 1 and 2, titrate a short-acting opioid combined with a long-acting opioid, such as
    - Morphine extended release
    - Oxycodone extended release
    - Fentanyl transdermal patch (should not be used for opioid-naive patients)
  - Refer patients with escalating doses or adverse effects to a specialist in palliative medicine or anesthesia pain

Basic Opioid Management: Pearls

Initial pain medication selection should be based on patient-specific factors and drug availability. Patients with substantial renal impairment should avoid morphine products, given the possibility of rapid accumulation of metabolites that can lead to neurotoxicity.

For patients who have never received an opioid (opioid-naive patients), treatment should start with low doses of short-acting opioids (eg, morphine, oxycodone, hydromorphone) and close monitoring for efficacy and adverse effects (Table 33.1). For patients already taking opioids, the total amount of opioid taken in the preceding 24 hours should be calculated. An immediate-release form of opioid equivalent to 10% to 20% of the 24-hour total amount should be administered as the initial dose.

When therapy is rotated among the various opioids, validated equivalency charts should be used (Table 33.2). A common practice is the reduction in dose of the calculated opioid by 25% to 50% to account for individual variability and incomplete tolerance to the new medication.

For a patient requiring long-acting opioids for basal analgesia, the patient's total 24-hour use of short-acting opioids should be calculated. A basal agent is often started at a dose that is 50% of the 24-hour total.

Adverse Effects of Opioids

Adverse effects of opioid use include sedation, nausea, constipation, respiratory depression, and myoclonus. Appropriate opioid use for a serious illness should not lead to respiratory depression. An excessive dose of opioids or other patient factors can cause overdose and respiratory depression. Yet, respiratory depression is typically preceded by sedation. Somnolent patients with a reduced respiratory rate require close monitoring, dose reduction or discontinuation, review of concurrently used medications (eg, benzodiazepines), and occasionally, even administration of opioid-reversal agents, such as naloxone.

Tolerance to opioid-associated sedation and nausea typically develops within a few days of therapy initiation. For persistent nausea, opioid rotation and antidopaminergic antiemetics (eg, prochlorperazine, haloperidol, metoclopramide) are commonly used on a scheduled basis, rather than an as-needed basis. For opioid-associated constipation, colonic stimulants (eg, senna, bisacodyl) and osmotic agents (eg, polyethylene glycol, lactulose) are first-line medications. Fiber and bulking agents should be avoided in the presence of opioid-induced constipation; they can worsen symptoms, particularly when patients have inadequate fluid intake.

Patients who have serious and intolerable adverse effects to oral opioid medications may benefit from referral for interventional procedures, such as placement of intrathecal pumps or neurolytic blocks.

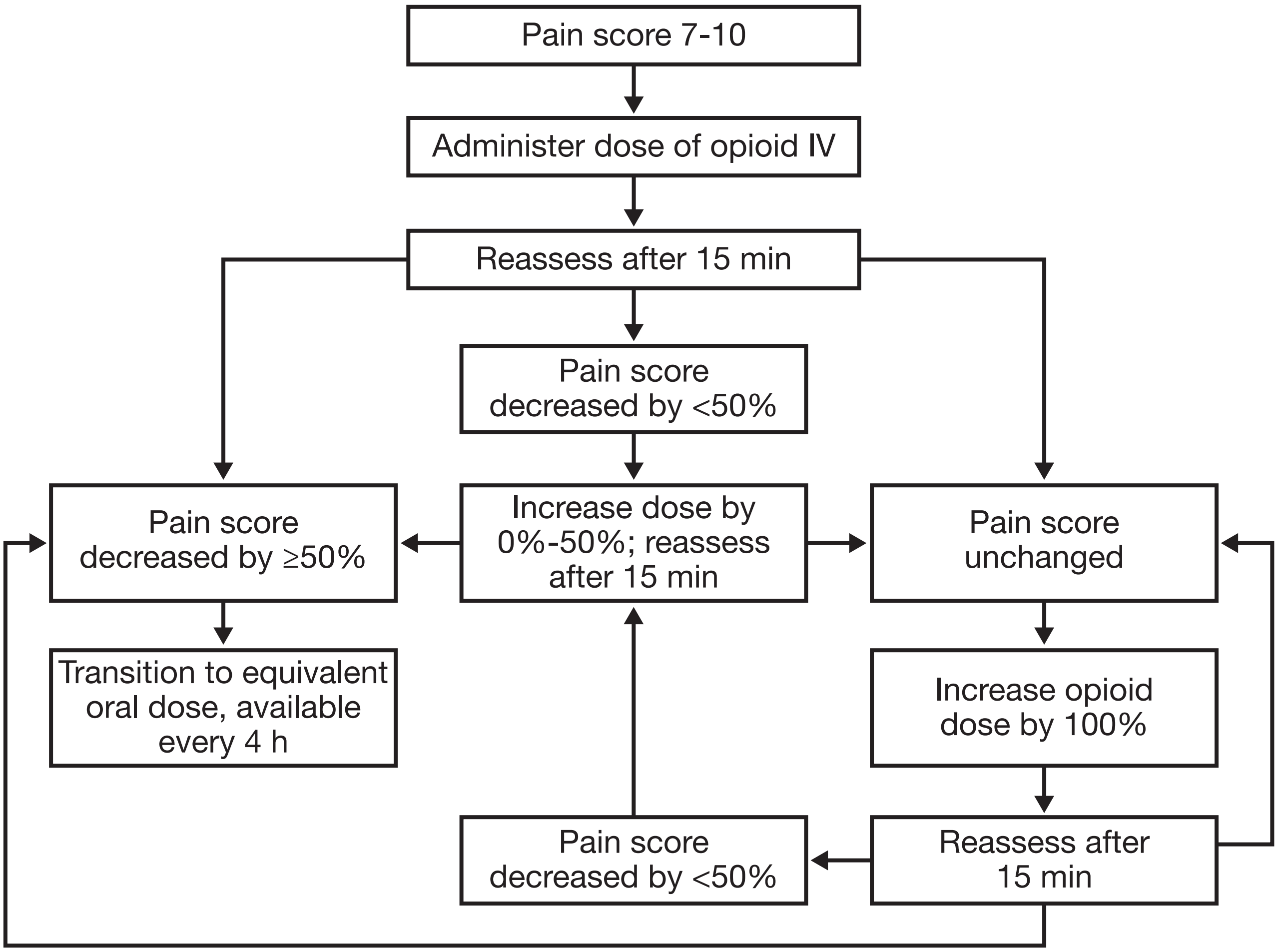
Pain score 7-10
Administer dose of opioid IV
Reassess after 15 min
Pain score decreased by <50%
Pain score decreased by ≥50%
Increase dose by 0%-50%; reassess after 15 min
Pain score unchanged
Transition to equivalent oral dose, available every 4 h
Increase opioid dose by 100%
Pain score decreased by <50%
Reassess after 15 min

Figure 33.1. *Algorithm for Treatment of Severe Cancer Pain With Intravenous Opioids. Dose of opioid should be determined by the patient's level of tolerance and previous use. IV indicates intravenous.*

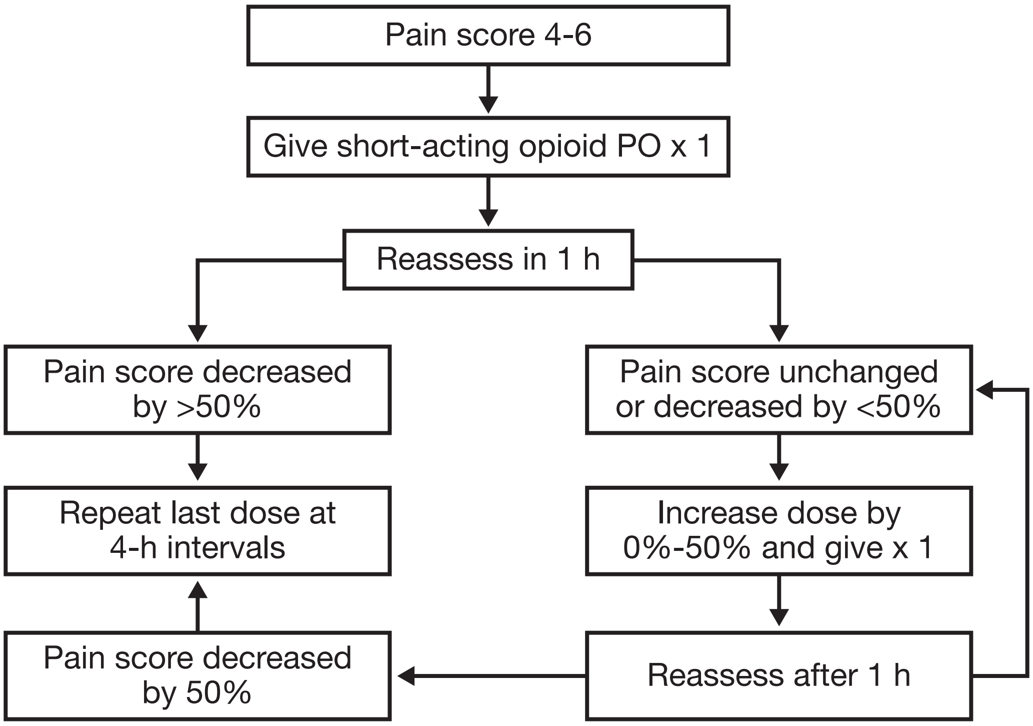
Pain score 4-6
Give short-acting opioid PO x 1
Reassess in 1 h
Pain score decreased by >50%
Pain score unchanged or decreased by <50%
Repeat last dose at 4-h intervals
Increase dose by 0%-50% and give x 1
Pain score decreased by 50%
Reassess after 1 h

Figure 33.2. *Algorithm for Treatment of Moderate Cancer Pain With Oral Opioids. PO indicates orally.*

Table 33.1 • Starting Doses for Opioid-Naive Patients

Opioid	Dose
Oral	
Oxycodone	2.5-5 mg
Morphine	5-7.5 mg
Hydromorphone	2 mg
Intravenous	
Morphine	2-4 mg
Hydromorphone	0.4 mg
Fentanyl	25 mcg

KEY FACTS

- ✓ Up to 50% of patients receiving therapy for cancer have cancer-related pain
- ✓ Physician barriers to optimal pain management—inadequate pain assessment, inadequate knowledge about safe opioid use, and reluctance to use opioids
- ✓ Opioids—most commonly used in the oral form to treat mild-to-moderate cancer-related pain
- ✓ Morphine—should be avoided for patients with marked renal impairment because metabolites can accumulate rapidly, leading to neurotoxicity

Principles of Palliative Care

Palliative care aims to reduce the pain and symptoms of patients with serious illness while working to improve the quality of life for them and their families. The focus is to delineate a patient's goals, values, and preferences while attempting to align medical care delivery with these goals. Early integration of palliative care in a number of illnesses (eg, cancer, heart failure) has been found to improve quality of life, reduce psychological comorbidity, and enhance patient and caregiver satisfaction with care. Subspecialty palliative care can be used for complex symptom management and challenging communication encounters.

All patients facing a serious illness can be candidates for palliative care, regardless of their current treatments or stage of illness. Palliative care involvement has been associated with improved quality of life without a decrement in survival and perhaps with even improved survival in some cases.

Table 33.2 • Opioid Equivalencies

Opioid	Oral	IV or SQ
Morphine	30 mg	10 mg
Oxycodone	20 mg	NA
Hydromorphone	7.5 mg	1.5 mg
Fentanyl	NA	100 mcg

Abbreviations: IV, intravenous; NA, not available; SQ, subcutaneous.

Ethical Care at the End of Life

Goals of Care

Clinicians need to communicate with their patients to ensure that the medical plan of care meets a patient's goals, values, and preferences whenever possible. Such conversations allow patients to be engaged in decision making to the degree they are able, and the dialog promotes patient autonomy. Effective in 2016, voluntary advance care planning discussions—and the documentation of such discussions—are recognized as a billable service by the Centers for Medicare & Medicaid Services. Characteristics of effective goals-of-care conversations are listed in Box 33.2.

Patients Who Do Not Have Decision-Making Capacity

The US Patient Self-Determination Act was passed in 1991 to ensure that patients are informed of their rights to accept or refuse medical interventions and to create and execute an **advance directive**. This act requires that hospitals, nursing homes, hospices, managed care organizations, and home health care agencies provide this information to patients at the time of admission or enrollment.

An advance directive is a document in which a person either states choices for medical treatments and designates an individual to make treatment choices when the person does not have decision-making capacity. The term *advance directive* also can apply to oral statements from a patient to caregivers, given when the patient was decisionally capable. Oral statements to a physician regarding a patient's desires should be recorded in the health record at the time of the communication. Advance directives may take various forms (Box 33.3).

Advance Directives: Pearls

Laws concerning advance directives differ from jurisdiction to jurisdiction. Physicians should be familiar with their local statutes.

Box 33.2 • Effective Goals-of-Care Conversations

Require appropriate context and prognostic awareness on the part of the patient

Occur early, when the patient is not struggling with acute illness

Continue on an iterative basis as the patient's goals and medical situation change

Are grounded in patient preferences and values, including psychosocial and spiritual beliefs

Require guidance and recommendations from clinicians

Include surrogate decision makers when possible

Box 33.3 • Various Forms of Advance Directives

Living will

Durable power of attorney for health care (DPAHC)

A document appointing a health care surrogate (in jurisdictions that do not formally recognize a DPAHC)

Disease- or treatment-specific directive

Health care directive that combines elements of the living will and the DPAHC

Activation of a traditional living will, also called an advance directive, requires that the patient be terminally ill and not have decision-making capacity. The traditional living will provides guidance to surrogate decision makers regarding goals and preferences for or against medical treatments. It may have limited effectiveness in aiding complex medical decision making if the patient is unable to make decisions but is not terminally ill (definition may vary by jurisdiction) or if the living will contains vague language.

The **durable power of attorney for health care** is a document that simply designates a surrogate decision maker, should a patient lose decision-making capacity. It often is combined with a living will that provides information to the patient's surrogate decision makers about patient preference for or against certain forms of therapy. Effective advance directives focus on the patient's goals, identify when the patient's quality of life may not be acceptable to the patient, and provide information about end-of-life preferences.

A treatment-specific medical care directive is useful for patients who have the specific desire never to receive certain forms of therapy. For instance, a Jehovah's Witness may use this directive to state a refusal for blood transfusion or blood products.

Key Definition

Advance directive: *a document in which a person states choices for medical treatments (a living will) and designates an individual who should make treatment choices when the patient does not possess decision-making capacity (durable power of attorney for health care).*

Key Definition

Durable power of attorney for health care: *a document that legally designates a surrogate decision maker, should the patient lose decision-making capacity.*

Surrogate Decision Making

A surrogate is a person who represents a patient's interests and previously expressed wishes, should the patient be unable or unwilling to do so for themselves. Ideally, the surrogate is designated by the patient and is documented in an advance directive before the patient loses decisional capacity. When a surrogate decision maker has not been identified, health care providers and family members must work within state statutes to identify appropriate parties to make decisions on the patient's behalf. Statutes differ from state to state, and providers should be familiar with the regulations within their practice area. Optimally, one is able to identify a person who knows the patient well and has the patient's interests at heart. When a surrogate cannot be identified through these means, it is sometimes necessary to engage the support of ethics consultants, legal services, or the courts.

In the absence of an explicit directive, a surrogate should make decisions to the best of their ability, based on the patient's beliefs and values. Application of choices that a patient would make if the patient were able to speak for themselves (and not necessarily what the surrogate would choose) is called *substituted judgment*. Sometimes, the surrogate may not have engaged in adequate communication with the patient to be able to project how the patient would decide. In these circumstances, the surrogate's and clinician's obligations are to try to decide in the patient's best interest, with use of the best interest standard.

Patients also may delegate decision making to a surrogate even while the patients still possess decisional capacity. This situation arises in certain cultural contexts in which decision-making authority is given to a certain member of the family or to a community leader. In respect to the patient's autonomy, the individual accepts this delegation of decision making.

At times, a surrogate's decisions or instructions to physicians conflict with a patient's previously expressed directive or with those of other family members. Because a physician's primary responsibility is to the patient, the physician should determine as best as possible what the patient would choose. When the physician is unable to resolve the conflict, involvement of an independent third-party arbitrator may be helpful, such as an ethics consultant or a legal counsel. After what the patient would want has been established, the treating physician has the obligation to comply with those wishes, even if the surrogate disagrees. The directive can be overruled only if clear evidence can be provided that the advance directive does not reflect what the patient really desired.

Withholding and Withdrawing Life-Sustaining Treatments

The transition from full therapeutic efforts against illness to comfort care for patients approaching death can be difficult. Nevertheless, compassionate, ongoing care for patients at the end of life is critical. Carrying out patients' requests to withhold or withdraw unwanted medical treatments is legal and ethical, and it is not the same as physician aid-in-dying or euthanasia. In

Table 33.3 • Options at the End of Life: How Do They Differ?

	Option				
	Life-Sustaining Treatment				
Characteristic	**Withhold**	**Withdraw**	**Palliative Sedation and Analgesia**	**Physician Aid-In-Dying**	**Euthanasia**
Cause of death	Underlying disease	Underlying disease	Underlying disease[a]	Intervention prescribed by physician and used by patient	Intervention used by physician
Intent or goal of intervention	Avoidance of burdensome intervention	Removal of burdensome intervention	Relief of symptoms	Termination of patient's life	Termination of patient's life
Legal?	Yes[b]	Yes[b]	Yes	Differs by state[c]	No

[a] Palliative sedation and analgesia may hasten death (so-called double effect).

[b] Several states limit the power of surrogate decision makers regarding life-sustaining treatment.

[c] Legal only in California, Colorado, Montana, Oregon, Vermont, Washington, and District of Columbia (at the time of publication).

physician aid-in-dying, a patient personally terminates their life by using an external means provided by a clinician (eg, a lethal prescription). In euthanasia, the clinician directly terminates the patient's life (eg, a lethal injection). In physician aid-in-dying and euthanasia, a new intervention is introduced (eg, medication) with the sole intention of the patient's death. In contrast, when a patient dies after an intervention is withheld or withdrawn, the underlying disease is the cause of death (Table 33.3). The intent of withholding an undesired intervention or therapy is freedom from treatments perceived as burdensome.

The right to refuse medical treatments is not a right to die, as it has been frequently described, but rather a right to be left alone or a freedom from unwanted touching. Notably, there is no ethical or legal distinction between withholding treatment in the first place and withdrawing a treatment after it has been begun. The right of a decisionally capable person to refuse artificial hydration and nutrition was upheld by the US Supreme Court. In contrast, a surrogate decision maker's right to refuse treatment for a decisionally incapable person may have restrictions in some states. Certain states require clear and convincing evidence that withholding or withdrawal of life-sustaining treatment would be the patient's desire. The value of each medical therapy (a benefit to burden ratio) should be assessed for each patient. When appropriate, withholding or withdrawing life support is best accomplished with input from more than 1 experienced clinician. These topics, along with other ethical considerations, are discussed in Chapter 30, "Medical Ethics."

Do-Not-Resuscitate Orders

Do-not-resuscitate (DNR) orders affect only the administration of cardiopulmonary resuscitation (CPR). Other therapeutic options are not influenced by the order. A DNR order can be compatible with maximal forms of treatment (eg, elective intubation, elective cardioversion, surgical procedure). Every person whose medical history is unclear or unavailable should receive CPR in the event of cardiopulmonary arrest.

Futility of or Demands for Nonbeneficial Interventions

Patients have the right to *refuse* any and all medical therapies, but the principle of respect for autonomy does not give patients—or their surrogates—the right to *demand* particular treatments. Such concerns can arise when patients or families request treatments that have little chance of resulting in survival or meaningful recovery. They also can happen when a clinician feels compelled to consider unilaterally withholding or withdrawing medical interventions. Conflict between patient autonomy and the professional judgment, moral autonomy, and integrity of the caregivers can occur, and as moral agents, physicians should not be forced to violate their ethical beliefs.

KEY FACTS

- ✓ Palliative care—appropriate for all patients with serious illness and may improve survival for some patients
- ✓ Withholding or withdrawing treatments at a patient's request is not morally the same as physician aid-in-dying
- ✓ DNR orders—apply only to CPR, not to other therapeutic options
- ✓ Although patients can refuse any and all therapies, patient autonomy should not be interpreted as a right to any and all medical therapies or interventions. Clinicians are not obligated to provide medically inappropriate care and have an ethical responsibility to be an active participant in shared decision making with patients. In addition, clinicians are under no obligation to grant all requests demanded by patients

34

Physician Well-Being and Burnout[a]

BRIANNA E. VAA STELLING, MD; COLIN P. WEST, MD, PHD

Professional burnout is a work-related syndrome of depersonalization, emotional exhaustion, and decreased sense of personal accomplishment. Among US physicians, burnout has reached epidemic levels, and approximately 50% of practicing physicians meet its criteria. Burnout has grave personal consequences, including decreased quality of life, higher rates of depression, and suicidal ideation. In health care, professional burnout affects patient safety, physician turnover, and patient satisfaction. Given these undesirable outcomes, many medical institutions have increased their efforts to target burnout and improve physician well-being and have made it an important focus.

Key Definition

Burnout: *a work-related syndrome of depersonalization, emotional exhaustion, and decreased sense of personal accomplishment.*

Epidemiologic Factors of Burnout

When does burnout begin? Are the high rates of physician burnout a consequence of the medical practice self-selecting persons with a predisposition or tendency to have burnout? Research has shown that matriculating medical students have lower rates of burnout and depression and higher quality of life than population-based control students graduating with a 4-year college degree. However, when surveyed during their medical school training, they report higher rates of burnout, depression, and fatigue than the control students, indicating that burnout emerges in medical school.

Burnout intensifies during residency, with average burnout rates between 50% and 76% reported in the literature. Burnout during this training leads to important consequences, including suboptimal patient care, increased self-perceived errors, and decreased quality of life. Similar to the phenomenon seen in medical students, residents have substantially higher rates of burnout, depression, and fatigue compared with population-based controls. They also have lower mental, physical, and emotional quality of life.

Because of the prevalence of burnout among medical residents, the 2017 Accreditation Council for Graduate Medical Education (ACGME) Common Program Requirements introduced a section on resident well-being. In it, ACGME mandated that programs educate residents on the symptoms of burnout and provide appropriate resources for those with burnout. Furthermore, the ACGME Clinical Learning Environment Review Program currently outlines an expectation that institutions measure resident burnout annually. Numerous residency programs are adopting wellness programs, with a focus on integrating well-being topics into the curriculum. Other strategies include stress management workshops, resiliency training, and Balint groups aimed at promoting self-reflection and interconnectedness. Balint groups are groups where physicians present cases and discuss the physician-patient interaction.

When it comes to practicing physicians, national studies indicate that approximately 50% of US physicians have notable burnout symptoms. Unfortunately, the problem seems to be getting worse, with a 10% increase in the prevalence of burnout among US physicians from 2011 to 2014. Burnout among US physicians is nearly double that seen in US workers in other fields. Furthermore, approximately 60% of US physicians are dissatisfied with their work-life balance compared with 36% of US nonphysician workers. This finding persists after adjustment for age, sex, relationship status, and hours worked per week.

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[a] Portions previously published in Shanafelt TD, Noseworthy JH. Mayo Clin Proc. 2017 Jan;92(1):129-146 and Shanafelt TD, Mungo M, Schmitgen J, Storz KA, Reeves D, Hayes SN, et al. Mayo Clin Proc. 2016 Apr;91(4):422-31; used with permission of Mayo Foundation for Medical Education and Research; and Shanafelt TD, West CP, Sloan JA, Novotny PJ, Poland GA, Menaker R, et al. Arch Intern Med. 2009 May 25;169(10):990-5; used with permission.

Multiple studies have investigated whether certain demographic characteristics are associated with burnout. In a national sample of more than 6,800 US physicians, researchers identified factors they found to be independently associated with burnout. These included age, sex, relationship status, hours worked per week, medical specialty, and practice setting. Female physicians were more likely than male physicians to experience burnout, and burnout was greater in early-career physicians (35 years of age and younger). Marriage seems to be protective against burnout. Physicians who practice in "front-line" specialties have burnout more commonly. These specialties include internal medicine, family medicine, and emergency medicine (Figure 34.1). Only 2 disciplines—ophthalmology and preventive and occupational medicine—report that more than one-half of their physicians are satisfied with their work-life balance.

Drivers of Burnout

Are physicians at inherent risk for burnout? Research has shown that physicians may have certain characteristics that predispose them to burnout. This so-called **physician personality** can be thought of as a triad of compulsiveness traits, composed of doubt, guilt, and an exaggerated sense of responsibility. Traits that make physicians excel, such as commitment to patients, diagnostic rigor, thoroughness, and desire to stay current, can turn maladaptive when physicians take on too much responsibility or set unrealistic expectations for themselves. Physicians should consistently reflect on their distinctive tendencies and consider the effect that these behaviors have on their overall well-being.

Key Definition

Physician personality: *a triad of compulsiveness traits composed of doubt, guilt, and an exaggerated sense of responsibility.*

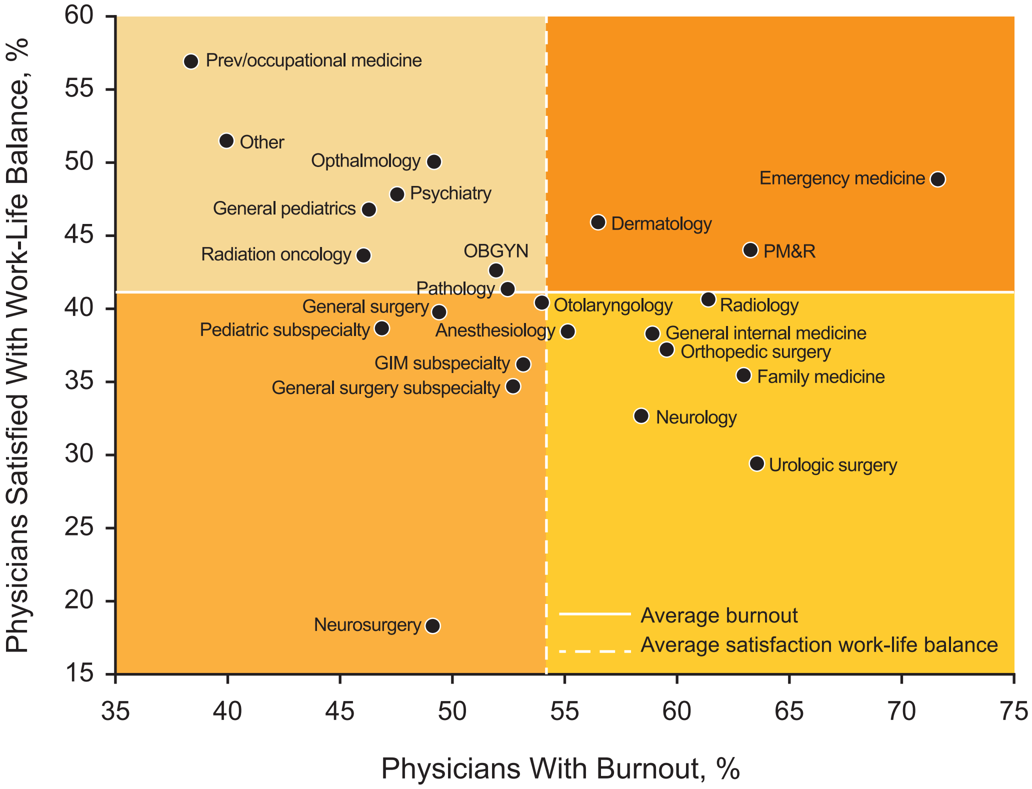

Figure 34.1. Burnout and Satisfaction With Work-Life Balance by Specialty in 2014. GIM indicates general internal medicine; OBGYN, obstetrics and gynecology; PM&R, physical medicine and rehabilitation; prev/occupational, preventive and occupational.

Modified from Shanafelt TD, Hasan O, Dyrbye LN, Sinsky C, Satele D, Sloan J, et al. Changes in Burnout and Satisfaction With Work-Life Balance in Physicians and the General US Working Population Between 2011 and 2014. Mayo Clin Proc. 2015 Dec;90(12):1600-13. Erratum in: Mayo Clin Proc. 2016 Feb;91(2):276; used with permission.

The work environment and the demanding nature of medical practice are 2 other key drivers of burnout. Many studies have identified the central factors of loss of autonomy, decreased control over the practice environment, and inefficient use of time due to administrative requirements. Other surveys have suggested the contributing factors of workload, sleep deprivation, lack of work-life balance, medical errors, risk of malpractice suits, and the methods physicians use to deal with patient death and illness.

A recent article published by authors, including the former president and chief executive officer of Mayo Clinic, categorized the drivers of professional burnout into 7 main dimensions: workload, efficiency, flexibility and control over work, work-life integration, alignment of individual and organizational values, social support and community at work, and degree of meaning derived from work. These dimensions are influenced by personal, work unit, organizational, and national factors.

Interestingly, research has shown a correlation between burnout and time spent engaged in the most meaningful work-related activity. In a study of more than 500 physicians, those who spent less than 20% of their time (approximately 1 workday per week) on the activity that is most meaningful to them had higher rates of burnout (53.8% vs 29.9%; $P<.001$). Moreover, time spent on the most meaningful activity was the strongest predictor of burnout in multivariate analysis (odds ratio, 2.75; $P=.001$). These findings suggest that efforts to optimize career fit may promote physician satisfaction while they reduce burnout.

Consequences of Burnout

Burnout has important consequences personally and professionally. On a personal level, burnout has been associated with substance abuse, depression, and suicidal ideation. Burnout also can negatively affect personal relationships and lead to marital discord. Studies have indicated that physician burnout influences quality of care and patient safety, with higher self-perceived rates of major medical errors reported by physicians who experience burnout. Physician distress has been linked to suboptimal prescribing habits, excessive test ordering, and risk of malpractice suits. Evidence exists that burnout affects the physician-patient relationship. Not surprisingly, patients of physicians who have higher professional satisfaction report higher satisfaction with their care.

KEY FACTS

- ✓ Factors in professional burnout—include age, sex, relationship status, and hours worked per week
- ✓ Personal consequences of professional burnout—greater risk of decreased quality of life, substance abuse, depression, suicidal ideation, and sleep deprivation
- ✓ Physician burnout affects quality of care and patient safety
- ✓ Central physician burnout factors—include loss of autonomy, decreased control over the medical practice environment, and inefficient use of time
- ✓ Marriage—appears to be protective against burnout
- ✓ Burnout assessment—should occur at individual and organizational levels
- ✓ Solutions to physician burnout—require coordinated efforts at national and, potentially, international levels of medical institutions

Burnout and professional satisfaction have been linked recently to professional effort and physician turnover. Beginning in 2008, practicing physicians at all 3 Mayo Clinic campuses were longitudinally monitored over 6 years, with assessments of burnout, satisfaction, and full-time or part-time work status. Collectively, high burnout and low satisfaction correlated with a reduction in full-time employment (FTE) (ie, work effort) over the following 24 months. In longitudinal analysis at the individual physician level, each 1-point increase in the 7-point emotional exhaustion scale was associated with a 43% increase in the odds of FTE reduction over the following 24 months. In addition, each 1-point decrease in the 5-point satisfaction score (Box 34.1) was associated with odds that were 34% greater for reduction in FTE over the following 24 months. A recent national survey of nearly 7,000 US physicians reported similar results, showing that burnout, dissatisfaction with work-life integration, and dissatisfaction with the electronic health record were independent predictors of intent to reduce clinical work hours or leave practice. Given the cost of replacing a physician, estimated to be at least 2 to 3 times the physician's annual salary, these findings pose a substantial financial threat to society.

Box 34.1 • Job Satisfaction 5-Point Likert Scale

Question

Considering everything, how would you rate your overall satisfaction with Mayo Clinic as a whole at the present time?

Answer

Very satisfied	5
Satisfied	4
Neither satisfied nor dissatisfied	3
Dissatisfied	2
Very dissatisfied	1

Strategies to Reduce Burnout and Improve Well-being

Individual-focused and structural or organizational solutions are required to address physician burnout, and a growing body of evidence confirms that both approaches can be effective. These methods generally align with the recognized drivers of burnout previously described. Importantly, not only do both approaches offer at least modest benefit, but both also are necessary. Addressing physician burnout should be viewed as a shared responsibility across health care systems, organizations, institutions, and individual physicians.

Evidence-based strategies usable by individual physicians include mindfulness-based stress reduction, stress management training, communication skills training, exercise programs and self-care efforts, and participation in small-group programs oriented around promotion of community, connectedness, and meaning. Organizational strategies have proven more difficult to study to date, but in the United States, restrictions on resident duty hours have modestly reduced burnout rates among trainees. Additional studies have shown benefit from reduction in physician practice hours in intensive care units and on teaching rotations. These approaches align with excessive workload as a driver of burnout. Locally developed practice changes to promote efficiency and satisfaction have shown benefit as well.

Additional interventions informed by cross-sectional research may offer benefit. Although data on the effect of these interventions are lacking, benefits might be expected from specific attention to career fit, the integration of work and home responsibilities, and reflection on personal values and how one's work aligns with those values. More broadly, health care organizations should consider specific strategies to promote physician well-being and address burnout. These strategies have been published in alignment with the previously noted 7 categories of drivers and generally extend the approaches already discussed (Table 34.1).

Table 34.1 • Examples of Individual and Organizational Strategies to Address Burnout

	Strategies	
Work Characteristic	**Individual**	**Organizational**
Workload	Part-time status	Productivity targets Duty hour requirements Integrated career development
Work efficiency/support	Efficiency/skills training	Electronic health record (±?) Staff support
Work-home integration/balance	Self-care Mindfulness	Meeting schedules Off-hours clinics Curricula during work hours Financial support/counseling
Autonomy/flexibility control	Stress management/resiliency Mindfulness Engagement	Physician engagement
Meaning/values	Positive psychology Reflection/self-awareness Mindfulness Small-group approaches	Core values Protect time with patients Promote community Work/learning climate

Regardless of the approach taken by health care organizations to address burnout, a valid assessment of physician burnout is required. Measurement should occur at the individual and organizational levels. Anonymous online tools exist that allow individual physicians to privately gauge their level of burnout against normative physician samples. These tools have been shown to prompt reflection and action steps to address burnout in large groups of physicians. At the organizational level, burnout assessment should be considered part of the "dashboard" of tracked institutional performance measures, quality indicators, and leadership performance. Such organizational assessments can be aggregated by work units to afford actionable insights into local issues with burnout while maintaining physician confidentiality.

Finally, solutions to physician burnout require coordinated efforts at national and, potentially, international levels. Regulatory and documentation requirements, although well intended, often overburden physicians and distract them from direct patient care activities. Maintenance of the critical importance of patient safety and optimization of patient outcomes, while protecting the most meaningful work roles for physicians, must become complementary goals. This method has been characterized as a necessary expansion of the Triple Aim approach to improvement in health system performance (improvement of the health of populations, improvement of the experience of care, and reduction in per capita costs of health care). The approach can be be expanded to a **Quadruple Aim** that adds the goal of improvement in the work lives of health care professionals and their experience in providing care. Because physician burnout directly hinders health system performance, efforts to address burnout should be considered fundamental elements of national and global strategies to improve health care.

Key Definition

Quadruple Aim: *improvement of the health of populations, improvement of the experience of care, reduction in per capita costs of health care, and improvement in the work lives of health care professionals and their experience of providing care.*

Concluding Remarks

Physician burnout represents a public health crisis because of its high prevalence and serious consequences at all levels of the health care system. Physicians cannot provide optimal patient care when they are not well. Fortunately, the drivers of burnout and attendant solutions to reduce it and promote well-being are increasingly understood. With collaboration among individual physicians, health care organizations, and regulatory bodies, the field of medicine can achieve the desired goal of delivering outstanding patient care in a system where physicians experience joy in practice.

35

Preoperative Evaluation

BRIAN M. DOUGAN, MD; KARNA K. SUNDSTED, MD

Risks of Anesthesia and Surgery

The mortality rate associated with anesthesia and surgery has decreased markedly in the past several decades. Today, the overall mortality ratio is 1 in 250,000 cases, even though more complex surgical procedures are performed on sicker patients. The American Society of Anesthesiologists (ASA) classification, with its broadly defined categories, is used to estimate overall risk of death within 48 hours postoperatively (Table 35.1).

Neuraxial anesthesia and general anesthesia are not associated with substantially different outcomes for death and cardiac events. However, the type of surgery performed is an important determinant of cardiovascular morbidity and death. Yet, comorbid disease may outweigh the type of surgery in determining risk and predicting outcome.

Cardiac Risk Assessment and Risk Reduction Strategies

Perioperative death attributed to cardiac causes occurs in 1% to 2% of all surgical procedures. Perioperative myocardial infarction (MI) occurs in approximately 1% of general surgical procedures and in up to 3.2% of vascular surgical procedures. Among patients who have a perioperative MI, the hospital mortality rate is 15% to 25%. Those who survive to dismissal from the hospital have an increased risk of another MI and cardiovascular death for 1 year postoperatively.

Cardiac Risk Assessment

A stepwise approach is used for perioperative cardiac assessment, as outlined in the American College of Cardiology/American Heart Association (ACC/AHA) 2014 Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery (Figure 35.1). This guideline presents a framework for determining which patients are candidates for further testing on the basis of a risk estimate that incorporates both patient- and surgery-related risk factors.

Certain patient- and surgery-specific factors contribute to cardiac risk. The patient-specific risk factors include clinical predictors, medical history, and functional status. The surgery-specific risks are most often related to the urgency, duration, and type of surgical procedure.

KEY FACTS

- ✓ Overall mortality ratio associated with anesthesia and surgery is 1 in 250,000 cases
- ✓ Neuraxial anesthesia has no advantage over general anesthesia in terms of cardiac events and death
- ✓ Frequency of perioperative myocardial infarction—about 1% for general surgery and up to 3.2% for vascular surgery
- ✓ Cardiac risk assessment includes patient-specific factors (clinical predictors and functional status) and surgery-specific factors (surgical urgency, duration, and type)

The ACC/AHA guideline focuses on estimating the perioperative risk of a major adverse cardiac event through the

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The editors and authors acknowledge the contributions of Amy T. Wang, MD, and Karen F. Mauck, MD, to the previous edition of this chapter.

Table 35.1 • American Society of Anesthesiologists Classification of Anesthetic Death Within 48 Hours Postoperatively

Class	Physical Status	Death at 48 h
I	Healthy person younger than 80 y	0.07%
II	Mild systemic disease	0.24%
III	Severe but not incapacitating systemic disease	1.4%
IV	Incapacitating systemic disease that is a constant threat to life	7.5%
V	Moribund patient not expected to survive 24 hours, regardless of surgery	8.1%
E	Suffix added to any class to indicate emergency procedure	Doubles risk

Modified from Smith T, Pinnock C, Lin T, Jones R. Fundamentals of anaesthesia. 3rd ed. Cambridge (UK): Cambridge University Press; c2009; used with permission.

stratification of patients into either a group at low risk (≤1%) or one with elevated risk (>1%) on the basis of combined patient and surgical characteristics. This stratification scheme does not apply to patients who require an emergency operation or who have active cardiac conditions, including acute coronary syndrome, symptomatic heart failure, symptomatic valvular disease, or arrhythmias.

Clinical predictors of increased perioperative MI, heart failure, and death include active cardiac conditions and clinical risk factors (Boxes 35.1 and 35.2). The surgery-specific cardiac risk of a noncardiac surgical procedure is related to 2 important factors. The first is the type of surgery, which may identify a patient who has a greater likelihood of underlying heart disease (eg, vascular surgery) (Table 35.2). The second is the degree of hemodynamic cardiac stress associated with the surgery, which can be induced by pain, blood loss, and profound alterations in heart rate, blood pressure, and vascular volume.s

Functional capacity (Table 35.3) is estimated on the basis of the patient's history and is expressed in **metabolic equivalent tasks** (METs). One MET is a unit of sitting or resting oxygen uptake per kilogram of body weight per minute.

Key Definition

Metabolic equivalent task (MET): *1 MET is a unit of sitting or resting oxygen uptake per kilogram of body weight per minute.*

Patients with pulmonary hypertension undergoing noncardiac surgery should continue pulmonary vascular–targeted therapies such as phosphodiesterase type 5 inhibitors. Preoperative evaluation by a pulmonary hypertension specialist is advised for patients with pulmonary hypertension that has characteristics of high risk, including group 1 pulmonary hypertension (pulmonary arterial hypertension), pulmonary arterial systolic pressure greater than 70 mm Hg, moderate or greater right ventricular systolic dysfunction, and New York Heart Association class III or IV symptoms attributable to pulmonary hypertension.

Cardiac Risk Reduction Strategies

Evidence suggests that surgical or percutaneous revascularization is rarely indicated to decrease surgical risk, unless the intervention is indicated irrespective of the preoperative context. Percutaneous or surgical intervention is also associated with risk of adverse cardiac outcomes. Therefore, a morbidity and mortality advantage has not been shown for most patients when these interventions are performed before noncardiac surgery. The exception, however, is a patient who would have been referred for intervention irrespective of the preoperative context. In general, preoperative revascularization is beneficial for patients who have any of the following characteristics: 1) clinically important left main coronary artery disease; 2) 3-vessel disease; 3) 2-vessel disease with proximal involvement of the left anterior descending coronary artery; 4) coronary artery stenosis and either an ejection fraction less than 50% or demonstrable ischemia on noninvasive testing; 5) high-risk unstable angina or non–ST-segment elevation MI; or 6) acute ST-segment elevation MI.

The expected timing of the planned surgical procedure also needs to be considered in the decision on the type of revascularization procedure. Surgery performed within 30 days of coronary artery bypass grafting is associated with increased risk of postoperative cardiac complications. Percutaneous interventions with angioplasty alone or in conjunction with stent placement also require an appropriate course of dual antiplatelet therapy during the healing and reendothelialization of vessel injury.

β-Blockers have been reported to decrease the risk of perioperative cardiac complications for patients who are at risk. However, the topic is controversial because more recent data have shown mixed results. The current recommendations for perioperative β-blockade, based on the 2014 ACC/AHA guideline, are summarized in Box 35.3.

The 2014 ACC/AHA guideline also includes 3 recommendations for perioperative statin therapy. The first is continuation of statin therapy for patients taking these agents (class I). The second is consideration of initiation of statin therapy for patients undergoing vascular surgery (class IIa). The third is consideration of statin therapy initiation for patients who otherwise have clinical indications and are undergoing procedures that involve increased risk (class IIb).

Patients With Coronary Stents

The 2016 ACC/AHA Focused Update on Duration of Dual Antiplatelet Therapy for Patients With Coronary Artery

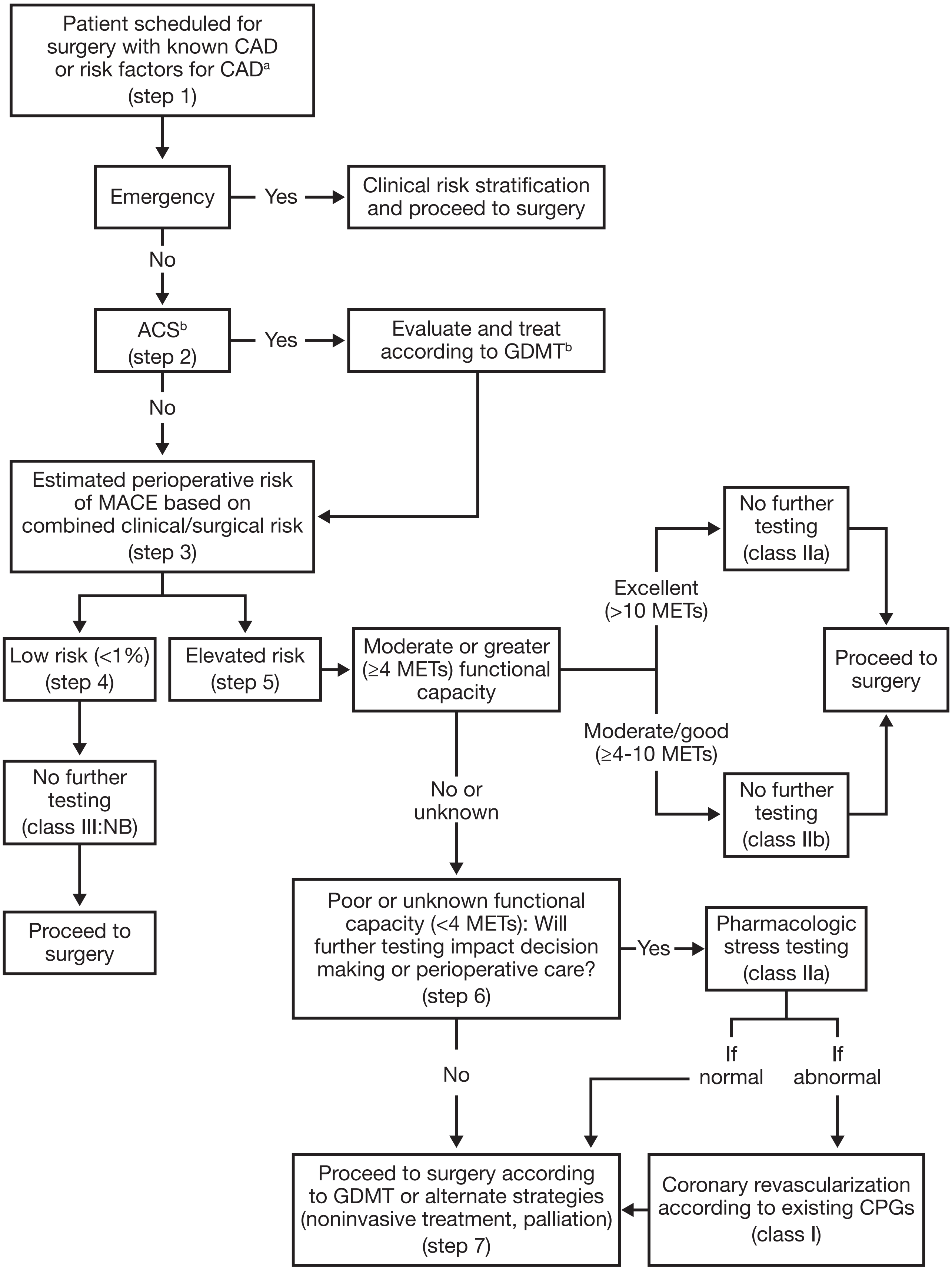
Patient scheduled for surgery with known CAD or risk factors for CAD[a] (step 1)
Emergency
Yes
Clinical risk stratification and proceed to surgery
No
ACS[b] (step 2)
Yes
Evaluate and treat according to GDMT[b]
No
Estimated perioperative risk of MACE based on combined clinical/surgical risk (step 3)
Low risk (<1%) (step 4)
Elevated risk (step 5)
No further testing (class III:NB)
Proceed to surgery
Moderate or greater (≥4 METs) functional capacity
Excellent (>10 METs)
No further testing (class IIa)
Proceed to surgery
Moderate/good (≥4-10 METs)
No further testing (class IIb)
No or unknown
Poor or unknown functional capacity (<4 METs): Will further testing impact decision making or perioperative care? (step 6)
Yes
Pharmacologic stress testing (class IIa)
If normal
If abnormal
No
Proceed to surgery according to GDMT or alternate strategies (noninvasive treatment, palliation) (step 7)
Coronary revascularization according to existing CPGs (class I)

Figure 35.1. Stepwise Approach to Perioperative Cardiac Assessment.

Box 35.1 • Active Cardiac Conditions

Heart failure
  Symptoms: dyspnea, orthopnea, paroxysmal nocturnal dyspnea
  Physical examination findings: peripheral edema, jugular venous distention, rales, third heart sound
  Imaging findings: chest radiograph showing pulmonary edema or pulmonary vascular redistribution
Valvular heart disease
  Clinically suspected moderate or severe valvular stenosis or regurgitation if no echocardiography within the past year or substantial change in clinical status or physical examination findings
Arrhythmias
  High-grade atrioventricular block
  Supraventricular arrhythmias if clinically unstable condition or uncontrolled ventricular rate
  Ventricular arrhythmias associated with structural heart disease, hemodynamic compromise, or inherited electrical disorders
Acute coronary syndromes
  Unstable angina
  Non–ST-segment myocardial infarction
  ST-segment myocardial infarction

Data from Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Dec 9;130(24):2215-45.

Box 35.2 • Revised Cardiac Risk Index (RCRI) and American College of Surgeons National Surgical Quality Improvement Program (NSQIP) Database

RCRI[a]
  High-risk surgery (intraperitoneal, intrathoracic, or suprainguinal vascular)
  History of ischemic heart disease
  History of compensated or prior heart failure
  History of cerebrovascular disease
  Diabetes mellitus with insulin treatment
  Renal insufficiency (creatinine >2.0 mg/dL)
NSQIP[b]
  Type of surgery
  Dependent functional status
  Abnormal creatinine level (>1.5 mg/dL)
  American Society of Anesthesiologists score
  Increased age (≥65 y)

[a] RCRI points and risk of major adverse cardiac event: 0 point, 0.4%; 1, 1.0%; 2, 2.4%; 3 or greater, 5.4%.

[b] Calculator is available at http://www.surgicalriskcalculator.com/miorcardiacarrest.

Data from Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 1999 Sep 7;100(10):1043-9 and Gupta PK, Gupta H, Sundaram A, Kaushik M, Fang X, Miller WJ, et al. Development and validation of a risk calculator for prediction of cardiac risk after surgery. Circulation. 2011 Jul 26;124(4):381-7.

Disease offers guidance on perioperative management of antiplatelet therapy. If a nonurgent elective procedure requires that P2Y12 inhibitor therapy be held, then dual antiplatelet therapy may be interrupted after 30 days with bare metal stent placement or at 6 months after drug-eluting stent placement. Dual antiplatelet therapy may be interrupted at 3 to 6 months if the risk of delayed surgery outweighs the risk of stent thrombosis (class IIb recommendation). If surgery is required within these time frames, then dual antiplatelet therapy should be continued unless the bleeding risk outweighs the risk of stent thrombosis. Aspirin therapy should be continued perioperatively and indefinitely unless bleeding risk is prohibitive.

Figure 35.1. *Continued*

Footnote a *indicates that recommendations for patients with symptomatic heart failure, valvular heart disease, or arrhythmias are discussed in sections 2.2, 2.4, and 2.5, respectively, of the article cited below. Footnote* b *indicates that clinical practice guidelines (CPGs) for ST-segment elevation myocardial infarction (STEMI) and for unstable angina/non-STEMI are listed in Table 2 of the article cited below. Class indicates class of recommendation: I, the benefit is much greater than the risk (the procedure should be performed); IIa, the benefit is greater than the risk (it is reasonable to perform the procedure); IIb, the benefit may be greater than or the same as the risk (the procedure may be considered); and III:NB, no benefit (the procedure is not helpful). ACS indicates acute coronary syndrome; CAD, coronary artery disease; GDMT, guideline-directed medical therapy; MACE, major adverse cardiac event; MET, metabolic equivalent task.*

(From Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Dec 9;130[24]:2215-45; used with permission.)

Table 35.2 • Cardiac Risk Stratification According to Surgical Procedure Type

Reported Cardiac Risk[a]	Procedure
High—often >5%	Emergent major operations, particularly in elderly persons Aortic and other major vascular procedures Peripheral vascular procedures Anticipated prolonged surgical procedures associated with large fluid shifts or blood loss (or both)
Intermediate—generally <5%	Carotid endarterectomy Head and neck operations Intraperitoneal and intrathoracic procedures Orthopedic procedures Prostate operations
Low—generally <1%[b]	Endoscopic procedures Superficial procedures Cataract extraction Breast operation

[a] Combined incidence of cardiac death and nonfatal myocardial infarction.

[b] Further preoperative cardiac testing is not generally required.

Data from Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. Circulation. 2007 Oct 23;116(17):e418-99. Epub 2007 Sep 27. Errata in: Circulation. 2008 Aug 26;118(9): e143-4. Circulation. 2008 Feb 5;117(5):e154.

KEY FACTS

- ✓ The only patients who need surgical or percutaneous intervention to reduce cardiac risk before surgery are those who would have had the intervention even if surgery was not planned
- ✓ Surgery within 30 days of coronary artery bypass grafting is associated with increased risk of postoperative cardiac complications
- ✓ Postponement of elective and nonurgent surgery after stent placement—30 days for bare metal stents and 365 days for drug-eluting stents
- ✓ After balloon angioplasty, elective and nonurgent surgery should be postponed for at least 14 days

Table 35.3 • Estimated Functional Capacity Requirements for Various Activities

Requirement	Activity (Can You . . .)
1 MET	Take care of yourself? Eat, dress, or use the toilet? Walk indoors around the house? Walk a block or 2 on level ground at 2-3 mph (3.2-4.8 kph)? Do light work around the house like dusting or washing dishes?
4 METs	Climb a flight of stairs or walk up a hill? Walk on level ground at 4 mph (6.4 kph)? Run a short distance? Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture? Participate in moderate recreational activities such as golf, bowling, dancing, doubles tennis, or throwing a baseball or football?
>10 METs	Participate in strenuous sports such as swimming, singles tennis, football, basketball, or skiing?

Abbreviations: kph, kilometers per hour; MET, metabolic equivalent task; mph, miles per hour.

Activities list from Hlatky MA, Boineau RE, Higginbotham MB, Lee KL, Mark DB, Califf RM, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). Am J Cardiol. 1989 Sep 15;64(10):651-4; used with permission.

Requirements data from Fletcher GF, Balady G, Froelicher VF, Hartley LH, Haskell WL, Pollock ML. Exercise standards. A statement for healthcare professionals from the American Heart Association. Writing Group. Circulation. 1995 Jan 15;91(2):580-615.

Pulmonary Risk Assessment and Risk Reduction Strategies

Pulmonary complications (respiratory failure, atelectasis, and pneumonia) are as common as cardiac complications for patients undergoing noncardiothoracic surgery, with rates between 1.2% and 10.9%, depending on ASA class. These complications account for an increase in hospital length of stay and in perioperative morbidity and death.

Pulmonary Risk Assessment

Data show an association between obstructive sleep apnea (OSA) and adverse perioperative outcomes, including acute respiratory failure, desaturation, and cardiac events. Previously,

Box 35.3 • Recommendations for Perioperative β-Blockade

- β-Blockade should not be started on the day of surgery
- For patients already taking a β-blocker, the drug should be continued without interruption perioperatively
- For patients with intermediate- or high-risk myocardial ischemia on preoperative testing, it may be reasonable to begin β-blockade perioperatively
- For patients with 3 or more Revised Cardiac Risk Index risk factors, it may be reasonable to begin β-blockade perioperatively
- For patients in whom β-blocker therapy is to be started before surgery, the drug should be started early enough to assess tolerability, preferably 2 to 7 days before surgery

Table 35.4 • Pulmonary Complication Risk Factors Used by Various Risk Calculators

Postoperative Respiratory Failure, Arozullah Respiratory Failure Index[a]	**Postoperative Pulmonary Failure, Gupta Calculator**[b]	**Postoperative Pneumonia, Gupta Calculator**[c]	**Postoperative Pulmonary Complications of Any Severity, ARISCAT (Canet) Risk Tool**[d]
Type of surgery and/or need for emergency surgery	Type of surgery	Type of surgery	Advanced age (>65 y)
SUN >30 mg/dL	Dependent functional status	Dependent functional status	Low preoperative oxygen saturation
Albumin <3.0 g/dL	Emergency case	COPD	Respiratory infection within the past month
Partially or fully dependent functional status	Preoperative sepsis	Preoperative sepsis	Preoperative anemia
COPD	ASA class	ASA class	Upper-abdominal or thoracic surgery
Age >60 y		Smoker before operation	Surgery lasting >2 h
		Type of operation	Emergency surgery
		Age	

Abbreviations: ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; SUN, serum urea nitrogen.

[a] Data from Arozullah AM, Daley J, Henderson WG, Khuri SF. Multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery. The National Veterans Administration Surgical Quality Improvement Program. Ann Surg. 2000 Aug;232(2):242-53.

[b] Data from Gupta H, Gupta PK, Fang X, Miller WJ, Cemaj S, Forse RA, et al. Development and validation of a risk calculator predicting postoperative respiratory failure. Chest. 2011 Nov;140(5):1207-15.

[c] Data from Gupta H, Gupta PK, Schuller D, Fang X, Miller WJ, Modrykamien A, et al. Development and validation of a risk calculator for predicting postoperative pneumonia. Mayo Clin Proc. 2013 Nov;88(11):1241-9.

[d] Data from Canet J, Gallart L, Gomar C, Paluzie G, Vallès J, Castillo J, et al; ARISCAT Group. Prediction of postoperative pulmonary complications in a population-based surgical cohort. Anesthesiology. 2010 Dec;113(6):1338-50.

OSA was shown to be associated with an increase in the number of unplanned intensive care unit transfers and in the hospital length of stay. Patients should be screened for OSA preoperatively. If increased risk is identified, the patient should be monitored with continuous pulse oximetry postoperatively. Alternatively, the patient may be referred to a sleep specialist for further evaluation and treatment preoperatively if time permits. All patients with OSA should be instructed to bring their continuous positive airway pressure (PAP) device to the hospital.

Although it seems intuitive that obesity, asthma, and restrictive lung disease would be associated with an increased incidence of perioperative pulmonary complications, there is not good evidence that this is the case. Clinical studies have not shown an increased risk of postoperative pulmonary complications for obese patients, even when they are morbidly obese. Patients with mild or moderate asthma have not been shown to have increased risk, and neither have patients with chronic restrictive lung disease or restrictive physiologic characteristics (neuromuscular disease or chest wall deformities). Patients who are taking inhaled medications should be instructed to continue their use in the perioperative period.

Risk calculators are available for postoperative respiratory failure, postoperative pneumonia, and postoperative pulmonary complications of any severity (Table 35.4). The calculators identify risk factors that contribute to pulmonary complications perioperatively, such as smoking, age, high ASA class, and surgery type. They provide clinicians with predictive tools, which may aid in early identification and intervention for postoperative pulmonary issues.

Risk Reduction Strategies

All patients who are identified as having increased risk of postoperative pulmonary complications should receive 2 interventions postoperatively. The interventions are deep breathing exercises or incentive spirometry (PAP for patients unable to perform these) and selective use of a nasogastric tube (as needed for postoperative nausea and vomiting, inability to tolerate oral intake, or symptomatic abdominal distention). For patients with suspected OSA, continuous postoperative pulse oximetry or apnea monitoring, or both, is recommended. Continuous PAP or bilevel PAP may be used if apnea is identified. Aspiration precautions should be implemented as appropriate.

Venous Thromboembolic Prophylaxis

Although all surgical patients are at increased risk for venous thrombosis (VTE) disease, certain patients form a high-risk subset. These patients include those who are elderly and those who have prolonged anesthesia, previous VTE disease, hereditary disorders of thrombosis, prolonged immobilization or paralysis, malignancy, obesity, varicosities, or oralharmacologic estrogen use.

The American College of Chest Physicians released the ninth edition of its antithrombotic therapy and prevention of thrombosis guidelines, which include updated guidelines on prevention of VTE disease in orthopedic and nonorthopedic surgery patients. For nonorthopedic surgery patients, the most recent guidelines include application of the updated **Caprini Risk Score** (Table 35.5 and Figure 35.2). This score offers an individualized VTE prophylaxis strategy based on patient comorbidities and risk of deep vein thrombosis. For orthopedic surgery patients, the new guidelines recommend use of both intermittent pneumatic compression devices

Table 35.5 • Application of Caprini Risk Score in Nonorthopedic Surgery Patients

Risk of DVT	Caprini Score	Recommended VTE Prophylaxis
Very low (<0.5%)	0	Early ambulation
Low (~1.5%)	1-2	IPC
Moderate (~3%)	3-4	LMWH, LDUH (3 times daily), or mechanical prophylaxis, preferably with IPC
High (~6%)	>5	LMWH or LDUH (3 times daily) in addition to mechanical prophylaxis
In relation to cancer		Extend for 4 wk

Abbreviations: DVT, deep vein thrombosis; IPC, intermittent pneumatic compression; LDUH, low-dose unfractionated heparin; LMWH, low-molecular-weight heparin; VTE, venous thromboembolic disease.

Data from Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al; American College of Chest Physicians. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e227S-77S. Erratum in: Chest. 2012 May;141(5):1369.

and an antithrombotic agent, with extension of thromboprophylaxis for at least 10 to 14 days and optimally for 35 days. Low-molecular-weight heparin is the agent of choice (Box 35.4).

Key Definition

***Caprini Risk Score:** a scoring system that offers an individualized prophylaxis strategy for venous thromboembolic disease on the basis of patient comorbidities and risk of deep vein thrombosis.*

Perioperative Medical Comorbidities

Liver, adrenal, or thyroid disease requires special consideration perioperatively. Patients with compensated liver disease are often able to proceed with surgery. However, those with severe liver disease and its complications are at increased risk.

Each Risk Factor Represents 1 Point

☐ Age 41-60 y
☐ Swollen legs (current)
☐ Varicose veins
☐ Obesity (BMI >25)
☐ Minor surgery planned
☐ Sepsis (<1 mo)
☐ Acute myocardial infarction
☐ Congestive heart failure (<1 mo)
☐ Medical patient currently at bed rest
☐ History of inflammatory bowel disease
☐ History of prior major surgery (<1 mo)
☐ Abnormal pulmonary function (COPD)
☐ Serious lung disease, including pneumonia (<1 mo)
☐ Oral contraceptives or hormone replacement therapy
☐ Pregnancy or postpartum (<1 mo)
☐ History of unexplained stillborn infant, recurrent spontaneous abortion (≥3), premature birth with toxemia, or growth-restricted infant
☐ Other risk factors ____________________

Subtotal:

Each Risk Factor Represents 2 Points

☐ Age 60-74 y
☐ Arthroscopic surgery
☐ Malignancy (present or previous)
☐ Laparoscopic surgery (>45 min)
☐ Patient confined to bed (>72 h)
☐ Immobilizing plaster cast (<1 mo)
☐ Central venous access
☐ Major surgery (>45 min)

Subtotal:

Each Risk Factor Represents 3 Points

☐ Age ≥75 y
☐ History of DVT/PE
☐ Positive factor V Leiden
☐ Family history of thrombosis*
☐ Positive prothrombin 20210A
☐ Positive lupus anticoagulant
☐ Elevated serum homocysteine level
☐ Heparin-induced thrombocytopenia (do not use heparin or any low-molecular-weight heparin)
☐ Elevated anticardiolipin antibodies level
☐ Other congenital or acquired thrombophilia

If yes: Type ____________________

*most frequently missed risk factor

Subtotal:

Each Risk Factor Represents 5 Points

☐ Stroke (<1 mo)
☐ Elective major lower extremity arthroplasty
☐ Hip, pelvis, or leg fracture (<1 mo)
☐ Acute spinal cord injury (paralysis) (<1 mo)
☐ Multiple trauma (<1 mo)

Subtotal:

Total Risk Factor Score:

Figure 35.2. *Caprini Risk Score. BMI indicates body mass index calculated as weight in kilograms divided by height in meters squared; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; PE, pulmonary embolism.*

(Modified from Caprini JA. Thrombosis risk assessment as a guide to quality patient care. Dis Mon. 2005 Feb-Mar;51[2-3]:70-8; used with permission.)

Box 35.4 • Pearls on VTE Prophylaxis

Inferior vena cava filters and periodic surveillance with venous compression ultrasonography should not be used for primary VTE monitoring and prevention

Patients undergoing an operation for hip or knee replacement, hip fracture, or cancer are at particularly high risk for VTE. Among these patient populations, prophylaxis is more aggressive and data suggest that prophylaxis should continue after hospital dismissal (up to 35 days)

Renal impairment should be considered when deciding on doses of low-molecular-weight heparin, fondaparinux, and other antithrombotic drugs that are renally excreted, particularly for elderly patients and those at high risk for bleeding. Many of these drugs are contraindicated for patients receiving dialysis

For all patients undergoing neuraxial anesthesia or analgesia, special caution is needed when using anticoagulants for DVT prophylaxis. It may be best to wait until the catheter is removed

Some patients should continue a prolonged course of DVT prophylaxis well after hospital dismissal. Patients undergoing major surgery for cancer require 4 to 6 weeks of prophylaxis postoperatively

Low-dose aspirin or fondaparinux therapy is preferred to no prophylaxis for general and intra-abdominal or pelvic surgical patients at high VTE risk (Caprini Risk Score >5) for whom heparin is contraindicated or unavailable and who are not at high risk for major bleeding

Mechanical prophylaxis, preferably with intermittent pneumatic compression, is recommended for patients at high risk for VTE for whom anticoagulation is contraindicated because of increased bleeding risk

Abbreviations: DVT, deep vein thrombosis; VTE, venous thromboembolism.

Table 35.6 • Preoperative Testing

Test	Indication
Coagulation studies	Medical conditions associated with impaired hemostasis (eg, liver disease, malnutrition) Anticoagulant therapy History or examination findings suggestive of an underlying coagulation disorder (eg, excessive bleeding with previous procedures)
Complete blood cell count	History of anemia or disease known to cause anemia (eg, chronic kidney disease) Surgical procedure associated with substantial blood loss Signs or symptoms, or both, of infection Disease or medication known to affect platelet or white blood cell count (eg, myeloproliferative disorder)
Creatinine	Consider for all patients older than 50 y History of disease that may affect creatinine (eg, chronic kidney disease, hypertension, heart failure, diabetes mellitus) Medication known to affect creatinine (eg, diuretic, angiotensin-converting enzyme inhibitor) Patients with liver disease (MELD calculation)
Fasting blood glucose	Rarely indicated except for patients who are at very high risk for diabetes mellitus, are taking corticosteroids, or have signs or symptoms, or both, of undiagnosed diabetes mellitus
Hemoglobin A_{1c}	All patients with diabetes mellitus
Electrolytes	All patients with history of renal dysfunction Medication known to affect electrolytes (eg, digoxin, diuretic, antihypertensive) Disease known to affect electrolytes (eg, heart failure, liver disease)
Liver function tests	Rarely needed History of liver disease for which results may affect decision to proceed with surgery
Urinalysis	Urologic procedures Procedures to implant prosthetic materials (eg, joint arthroplasty)
Electrocardiography	Cardiovascular signs or symptoms, or both Known coronary artery disease, symptomatic valvular disease, peripheral arterial disease, cerebrovascular disease, known structural heart disease High-risk procedure Intermediate-risk procedure and at least 1 clinical risk factor (Revised Cardiac Risk Index) Not indicated for patients undergoing low-risk procedures

Table 35.6 • Continued

Test	Indication
Transthoracic echocardiography	Dyspnea of unknown origin Patients who have heart failure with worsening dyspnea or change in clinical status Consider for patients with previously documented left ventricular dysfunction if no assessment within 1 y
Chest radiography	Pulmonary signs or symptoms
Pulmonary function tests	Rarely indicated Reasonable for patients with history of underlying pulmonary disease (eg, COPD) and whose function does not appear to be at baseline

Abbreviations: COPD, chronic obstructive pulmonary disease; MELD, Model for End-Stage Liver Disease.

The Model for End-Stage Liver Disease (MELD) score and the Child-Turcotte-Pugh (CTP) classification should be used to stratify patients for risk. Those with CTP class C and a MELD score greater than 15 are considered at high risk and are generally advised to avoid elective surgery. They often are referred for transplant evaluation before consideration for elective surgery.

Intermediate-risk patients should be referred to a hepatologist to optimize management of complications before consideration for surgery. Patients with hypothyroidism can generally proceed to surgery with continuation of levothyroxine therapy. Of importance, the thyrotropin (thyroid-stimulating hormone) level should be checked within 6 months of the surgical procedure. Guidelines differ on the specific corticosteroid dose and duration that place patients at risk for perioperative adrenal insufficiency. Yet, high-risk patients should be given stress doses of corticosteroids perioperatively. Intermediate-risk patients may be tested with morning cortisol measurement or cosyntropin stimulation test before surgery to determine the need for perioperative coverage.

Preoperative Testing Guidelines

Results of routine laboratory and diagnostic tests often have little effect on perioperative management and can result in increased costs and unnecessary surgical delay. Therefore, routine preoperative testing should not be obtained. Rather, testing should be directed for specific indications and the history and physical examination findings (Table 35.6). No data are available on how long previous laboratory results may be applied to the preoperative evaluation. The ASA task force suggests that results obtained within 6 months of surgery are acceptable if the medical history has not changed appreciably.

KEY FACTS

- ✓ Patients are as likely to have pulmonary complications as cardiac complications when undergoing noncardiothoracic surgery
- ✓ All patients at risk for postoperative pulmonary complications require deep breathing exercises or incentive spirometry after surgery
- ✓ Risk of venous thromboembolism is increased for all patients undergoing surgery
- ✓ Patients with liver, adrenal, or thyroid disease need special consideration before surgery
- ✓ Preoperative laboratory and diagnostic testing should not be routine; it may not alter patient care and may increase costs and delay surgery

36 Preventive Medicine

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Key Concepts in Preventive Medicine

Types of Prevention

Preventive medicine focuses on preventing disease and keeping patients healthy. It has primary, secondary, and tertiary levels. In the primary level, disease is prevented before it occurs (eg, immunization, use of condoms to prevent sexually transmitted diseases), in part through use of health counseling (Box 36.1). **Secondary prevention** involves the detection of preclinical disease for the start of early treatment, thereby resulting in better outcomes (eg, cancer screening, hypertension therapy to prevent cardiovascular disease). It includes screening for chronic disease among adults (Boxes 36.2 and 36.3). By comparison, tertiary prevention improves outcomes such as quality of life and disease progression for the patient's known disease (eg, aspirin use after myocardial infarction to decrease recurrence, rehabilitation after stroke).

Key Definition

Secondary prevention: *detection of preclinical disease to start early treatment for better outcomes.*

Bias in Preventive Screening

For screening tests to be used and interpreted effectively, sources of bias must be considered. *Volunteer bias* occurs when the trial population in the study of a screening test is not representative of the target population to be screened. This bias happens when study participants who volunteer for or comply with screening tests tend to be healthier than those who do not. *Lead-time bias* occurs when screened patients appear to live longer than unscreened patients because the time between early detection and clinical presentation of disease (lead time) is wrongly included in survival estimates.

Length-time bias arises most often in observational studies because indolent disease is much more likely to be detected by a screening test than aggressive, rapidly progressive disease. Therefore, study participants with screening-detected disease live longer than those with symptomatic presentation of disease because of the nature of the disease rather than the screening test itself. An extreme example of this bias is *overdiagnosis*, which occurs when an indolent, nonprogressive, or regressive disease is detected that would have never affected the person's life normally.

Features of an Ideal Screening Test

A useful screening test should have certain characteristics, including those of the disease, the screening test, and the patient (Box 36.4).

Routine Screening for Adults

All adults should be evaluated with a thorough history and physical examination, including a detailed review of systems, allergy and immunization history, use of medication (prescription, over-the-counter, herbal medicine, and dietary supplements), social history, and family history.

The editors and authors acknowledge the contributions of Lynne T. Shuster, MD, and Amy T. Wang, MD, to the previous edition of this chapter.

Box 36.1 • Routine Recommendations of Lifestyle Counseling

Tobacco: Stop use

Alcohol: Reduce harmful alcohol use

Dental health: Visit dental care provider regularly; brush and floss daily

Skin health: Use sunscreen

Physical activity: Participate in moderate-intensity physical activity for ≥150 min or more weekly and muscle-strengthening exercises at least twice weekly

Healthful dietary choices: Limit intake of saturated fats and processed foods and increase intake of vegetables, fruits, whole grains, and unsaturated fats

Injury prevention

- Wear a safety belt in vehicles
- Wear a helmet with motorcycles, all-terrain vehicles, and bicycles
- Practice home safety measures, including use of smoke detectors, setting of water heaters to <120°F, and weapon safety

Chemoprophylaxis

- Women of childbearing age should take a multivitamin with folic acid daily
- Weigh the risks and benefits of aspirin for primary prevention of cardiovascular events for adults at increased risk for coronary artery disease

Healthful aging

- Use routine inquiry and simple tests to screen for vision and hearing loss
- Evaluate for polypharmacy, fall risk, home safety, and elder abuse
- Discuss advance directives

Healthy Lifestyle and Behavioral Counseling

Healthy living and counseling can be a crucial part of the screening process. Recommendations for an adult's routine lifestyle and behavioral counseling include absolute risk reduction (Box 36.1).

Chronic Disease Screening

Recommendations for the screening of adults for chronic disease are outlined in Boxes 36.2 and 36.3.

Cancer Screening

Although efforts in cancer prevention, screening, and treatment have improved cancer mortality rates, cancer continues to be the second leading cause of death in the United States. The guidelines by various organizations are conflicting when it comes to cancer screening. The US Preventive Services Task Force (USPSTF) cancer screening recommendations are highlighted in Boxes 36.2 and 36.3. Decisions to screen and counsel about disease risks involve many specific patient factors.

Lung Cancer

Lung cancer is the second most common cancer and the leading cause of cancer death among men and women in the United States. Smoking is the leading preventable cause of cancer in the United States and is a leading cause of heart disease and stroke. For asymptomatic persons at average risk, no screening for lung cancer is currently recommended. For persons at high risk, screening should be stopped if a health problem develops that substantially limits a patient's life expectancy or the patient's ability or willingness to have curative lung surgery.

Key Definition

High risk of lung cancer: *Risk level for adults age 55 to 80 years with a 30 pack-year smoking history (current or former smokers who have quit within the past 15 years).*

Breast Cancer

In the United States, breast cancer is the most commonly diagnosed cancer in women and the second leading cause of cancer death in women. The lifetime risk is estimated at 1 in 8 women. The timing of initiation and the frequency of breast cancer screening are controversial. Screening mammography (Table 36.1) is associated with an overall relative risk reduction of 19% in breast cancer death (about 15% for women with age in the 40s, 16% for women in their 50s, and 32% for women in their 60s). Estimates cite that 10% to 30% of screening-detected breast cancers represent overdiagnosis.

KEY FACTS

- ✓ Patients screened for a disorder appear to live longer than patients who were not screened if survival estimates wrongly include the time between early detection and clinical presentation (lead-time bias)
- ✓ Overdiagnosis (length-time bias)—diagnosis of a disease that progresses too slowly to ever affect a person's life
- ✓ USPSTF recommendation of lung cancer screening for high-risk patients—annual low-dose chest computed tomography
- ✓ Potential harms of screening mammography—false-positive results and overdiagnosis

Box 36.2 • Screening for Men and Women With Chronic Disease

Routine Disease Screening	Men	Women
Abdominal aortic aneurysm	One-time abdominal ultrasonography for men age 65-75 y who have smoked more than 100 cigarettes	
Breast cancer		Age 40-49 y, start screening mammography; chosen through individualized decision Age 50-74 y, biennial screening mammography recommended Age 75 y or older, evidence is insufficient to assess benefits and harms of screening mammography Evidence is insufficient to recommend clinical breast examination for average-risk women of screening age[a]
Cervical cancer		The USPSTF recommends screening women age 21-65 y with cytologic evaluation (Pap smear) every 3 y Women age 30-65 y who want screening less frequently can be screened with cytologic evaluation and HPV testing every 5 y
Chlamydia and gonorrhea		Screening for all sexually active women age 24 y and younger and others at increased risk
Osteoporosis		Bone mineral density testing for women age 65 y and older and for high-risk women younger than 65 y
Prostate cancer	The USPSTF recommends against prostate-specific antigen screening Other organizations, including ACP, ACS, and AUA, recommend shared decision making for men starting from age 50-69 y (age range differs by organization)	

Abbreviations: ACP, American College of Physicians; ACS, American Cancer Society; AUA, American Urological Association; USPSTF, US Preventive Services Task Force.

[a] The recommendation is against breast self-examination because studies have found more imaging and biopsies for women in the self-examination group than for the control women.

Colorectal Cancer

Colorectal cancer is the second leading cause of cancer death and the fourth most commonly diagnosed cancer in the United States. Most colorectal tumors are thought to develop from adenomatous polyps over a 10-year period. The risk of a polyp becoming malignant is increased by the following characteristics: size greater than 10 mm; presence of high-grade dysplasia; villous or tubulovillous morphologic features; and presence of 3 or more polyps. Patients with a first-degree relative who received a diagnosis of colon cancer before age 60 years or with 2 first-degree relatives with the diagnosis at any age are considered at high risk for colon cancer. An algorithm for colorectal cancer screening is presented in Figure 36.1.

Prostate Cancer

In the United States, prostate cancer is the leading cancer diagnosis among men. It also is the second most common cause of cancer death among US men, accounting for 10% of male cancer deaths annually. The 5-year survival rate is 98.9%. Reviews of autopsy series have identified prostate cancer in 46% of men with age in the 50s, 70% of men in their 60s, and 83% of men in their 70s who died of other causes. The lifetime risk

Box 36.3 • Screening for Adults With Chronic Disease

Routine Disease Screening	Recommendations
Alcohol abuse	The USPSTF recommends annually screening for adults age 18 y and older
Colorectal cancer	Normal risk screening
	• Colonoscopy every 10 y
	• Flexible sigmoidoscopy every 5 y, with interval stool testing every 3 y
	• Fecal occult blood test or fecal immunochemical test annually
	• Double-contrast barium enema every 5 y
	• Computed tomography colonography every 5 y (sensitivity, 86%-92% depending on polyp size)
	At-risk screening
	• Family history of colon polyps or colon cancer in a first-degree relative or in 2 second-degree relatives: colonoscopy at age 40 y or at 10 y before the youngest case in the immediate family (whichever is first) and then every 5 y
	• Inflammatory bowel disease: colonoscopy 8 y after diagnosis if pancolitis (12-15 y if left-sided colitis) and then every 1-2 y
Diabetes mellitus	For overweight or obese adults age 40-70 y, screen for diabetes
	Screening for gestational diabetes during pregnancy after 24 weeks' gestation
Depression	For adults in the general population, screen for depression
Hepatitis B virus	Screen for hepatitis B virus infection in persons at high risk for infection
Hepatitis C virus	Screen for hepatitis C virus infection in persons at high risk for infection
	The USPSTF recommends a 1-time screen for adults born between 1945 and 1965
HIV	Screen persons age 15-65 y at least once for HIV infection
Hyperlipidemia	Routine screening is recommended every 5 y starting at age 35 y for men and age 45 y for women
	For persons with risk factors for CAD, start screening at age 20 y
Hypertension	Initial screening for adults age 18 y and older, obtaining ambulatory measurements for confirmation of hypertension before treatment
	After initial screen, annual blood pressure screening for adults older than 40 y and adults at increased risk for hypertension
	For adults age 18-39 y, screen every 3-5 y
Lung cancer	The USPSTF recommends annual low-dose chest computed tomography for lung cancer screening in high-risk patients. Screening should stop if a health problem develops that substantially limits the patient's life expectancy or the ability or willingness to have curative lung surgery
	Persons at high risk for lung cancer are age 55-80 y with a 30 pack-year smoking history (current or former smokers who have quit within the past 15 y).
Obesity	Body mass index calculation periodically
Tobacco	Screen all adults for tobacco abuse

Abbreviation: USPSTF, US Preventive Services Task Force.

of prostate cancer is estimated at 1 in 6 men. The USPSTF recommends against routine prostate-specific antigen screening for prostate cancer because of the small potential for benefit and a much greater chance of harm related to prostate cancer screening and subsequent treatment. Similarly, screening with digital rectal examination has not been proven to decrease the mortality rate of prostate cancer.

Cervical Cancer

Human papillomavirus (HPV) infection is essential to the development of cervical cancer. HPV types 16 and 18 are thought to be responsible for approximately 70% of cervical cancer cases. Cervical cancer screening has proved to be effective and has contributed to decreases of approximately 50% in cervical cancer incidence death since the 1980s. A vaccine is

Box 36.4 • Characteristics of an Ideal Screening Test

- Disease characteristics
  - Be common
  - Cause serious outcomes in morbidity and death
  - Have a long preclinical phase (providing time to give early treatment)
  - Have an effective and acceptable treatment that is readily available
- Test characteristics
  - Be safe, acceptable, and easy to perform
  - Be highly sensitive or have a complementary, highly specific confirmatory test, or both
  - Have an acceptable rate of false-positive results
  - Be inexpensive
- Patient characteristics
  - Be at risk for the specific condition
  - Have access to testing
  - Have adequate life expectancy and quality of life
  - Be likely to follow through with additional testing and treatment

available to decrease the risk of HPV infection. With increased immunization against the high-risk types of HPV, the anticipated effect is a decrease in not only cervical cancer but also in other malignancies associated with HPV infection.

KEY FACTS

- ✓ Prostate cancer—can be found in >80% of men in their seventh decade who died of other causes
- ✓ Harms from prostate cancer overdiagnosis and overtreatment—sexual dysfunction, urinary incontinence, radiation-induced bowel dysfunction, and complications of surgery
- ✓ USPSTF recommendations for cervical cancer screening—for women age 21 to 65 years, cytologic evaluation (Pap smear) every 3 years; for women age 30 to 65 who want less-frequent screening, cytologic evaluation and HPV testing every 5 years
- ✓ USPSTF recommends against HPV testing for women younger than 30 years
- ✓ Cervical cancer screening—can be stopped after hysterectomy for benign reasons and after age 65 years if prior screening was adequate and risk is low

Immunizations

Immunization is one of the greatest successes of modern medicine for its improvement in morbidity and death.

Immunity has 2 primary types. *Active immunity* occurs when antigen is presented to the host, who produces an immune response that lasts for years. By comparison, *passive immunity* develops when large amounts of preformed antibodies prevent or diminish the effect of infection (eg, tetanus immune globulin, hepatitis B immune globulin). This immune response lasts for months rather than years.

Types of Vaccines

Live virus vaccines are generally contraindicated for pregnant women and for persons who have severe immunocompromise or who are receiving immunosuppressive therapy such as high-dose corticosteroids. Examples of live virus vaccines include the measles-mumps-rubella (MMR) vaccine and the varicella virus vaccine.

Pregnancy should be avoided for 4 weeks after a woman receives live virus vaccines.

Inactivated vaccines are generally safe for pregnant women, for whom these vaccines are indicated. The inactivated vaccines are also safe for immunocompromised persons; however, the response may be decreased.

In general, if a vaccination series is interrupted, the series should be resumed as soon as possible. It does not have to be restarted to achieve the desired immunity.

Recommendations of the Advisory Committee on Immunization Practices

The Advisory Committee on Immunization Practices (ACIP), a group in the US Centers for Disease Control and Prevention (CDC), provides a schedule for recommended immunizations of adults age 19 years and older (Figure 36.2). In addition, the CDC offers a free-to-download smartphone app that contains the current recommended vaccine schedules (https://www.cdc.gov/vaccines/schedules/hcp/schedule-app.html).

Influenza Vaccination

Annual influenza vaccination is recommended for all adults. Multiple preparations are available, including inactivated influenza vaccines, recombinant influenza vaccines, and live attenuated influenza vaccines (LAIVs). Recommendations regarding appropriate vaccines are updated annually. For example, for the 2017-2018 influenza season, the LAIV was not recommended because of concerns regarding efficacy.

The possibility of egg allergy needs to be considered before the influenza vaccine is administered. If a person can eat scrambled eggs without an allergic reaction, then the chances are low that the person has an egg allergy. If a person has an egg allergy

Table 36.1 • Benefits of Regular Screening Mammography Over 10 Years

Age Group, y	Relative Risk (95% CI) With Screening Mammography	Absolute Risk Reduction With Screening Mammography	Breast Cancer Deaths Averted, No./10,000 Women	NNI to Avoid 1 Breast Cancer Death
40-49	0.85(0.75-0.96)	0.0005	5	1,904
50-59	0.86(0.75-0.99)	0.0007	10	1,339
60-69	0.68(0.54-0.87)	0.0027	42	377

Abbreviation: NNI, number needed to invite to screen.

that causes hives only, the person can receive any influenza vaccine that otherwise would have been appropriate.

For persons with other allergic reactions to eggs (eg, respiratory distress, angioedema), any influenza vaccine that otherwise would have been appropriate can be administered in a medical setting supervised by a physician who has expertise in the recognition and management of allergic conditions.

Tetanus-Diphtheria and Tetanus-Diphtheria-Acellular Pertussis Vaccines

The primary tetanus-diphtheria (Td) vaccination series should be completed in early childhood. Unvaccinated adults should receive the first 2 doses at least 4 weeks apart and the third dose at 6 to 12 months after the second dose. One of these 3 doses should be a tetanus-diphtheria-acellular pertussis (Tdap) vaccine.

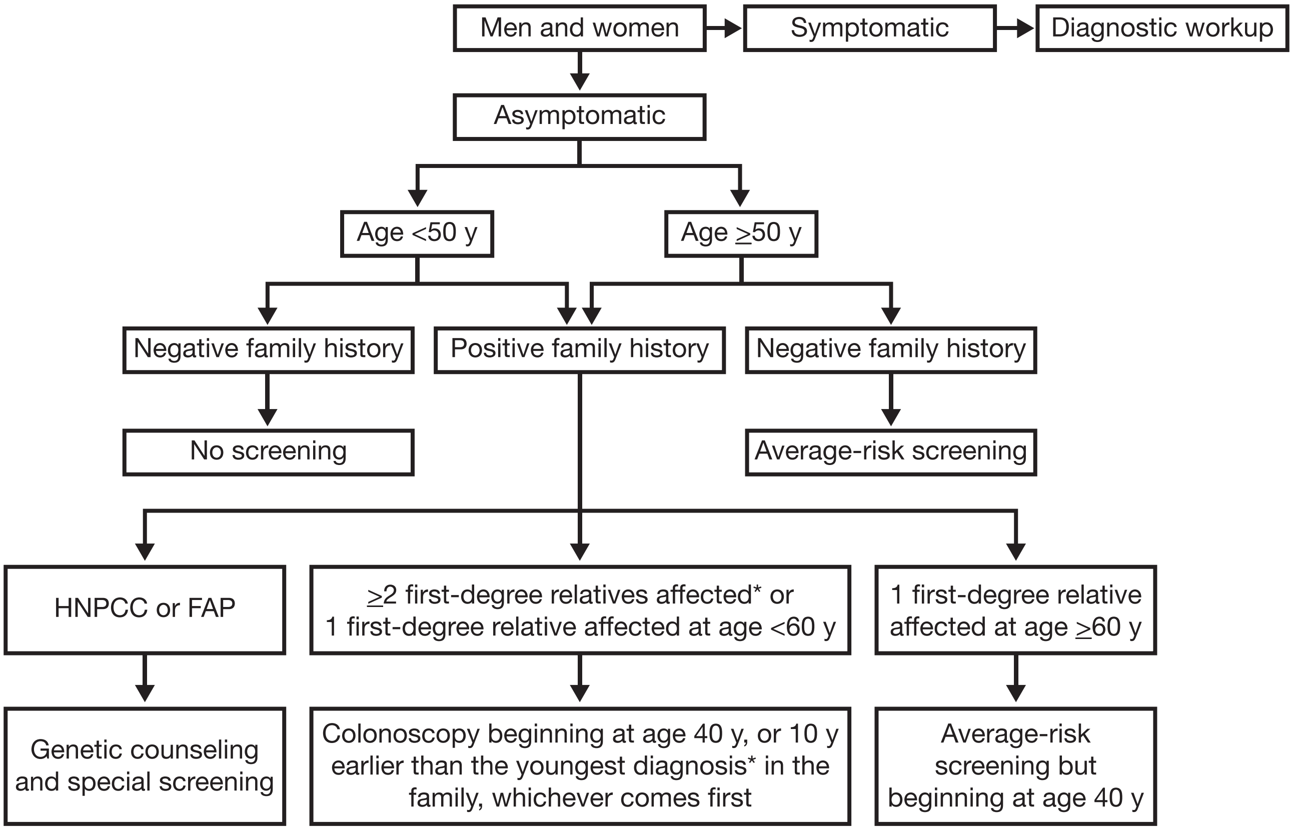
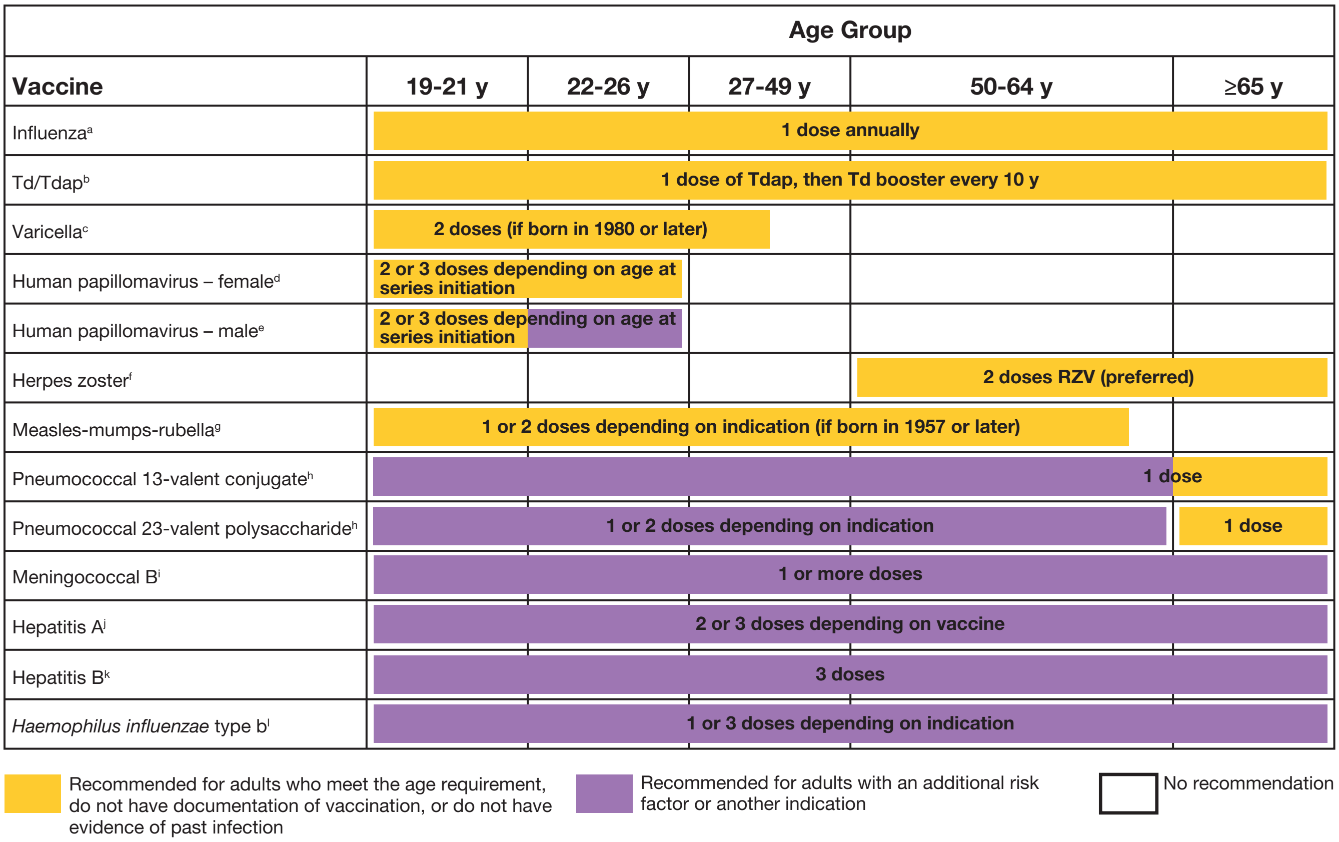

Men and women
Symptomatic
Diagnostic workup
Asymptomatic
Age <50 y
Age ≥50 y
Negative family history
Positive family history
Negative family history
No screening
Average-risk screening
HNPCC or FAP
≥2 first-degree relatives affected* or 1 first-degree relative affected at age <60 y
1 first-degree relative affected at age ≥60 y
Genetic counseling and special screening
Colonoscopy beginning at age 40 y, or 10 y earlier than the youngest diagnosis* in the family, whichever comes first
Average-risk screening but beginning at age 40 y

Figure 36.1. Algorithm for Colorectal Cancer Screening. See text for description of average-risk screening. Asterisk indicates either colorectal cancer or adenomatous polyp. FAP indicates familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colorectal cancer.

(From Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale—update based on new evidence. Gastroenterology. 2003 Feb;124[2]:544-60; used with permission.)



	Age Group				
Vaccine	**19-21 y**	**22-26 y**	**27-49 y**	**50-64 y**	**≥65 y**
Influenza[a]	🟨 **1 dose annually**	🟨	🟨	🟨	🟨
Td/Tdap[b]	🟨 **1 dose of Tdap, then Td booster every 10 y**	🟨	🟨	🟨	🟨
Varicella[c]	🟨 **2 doses (if born in 1980 or later)**	🟨	🟨		
Human papillomavirus – female[d]	🟨 **2 or 3 doses depending on age at series initiation**	🟨			
Human papillomavirus – male[e]	🟨 **2 or 3 doses depending on age at series initiation**	🟪			
Herpes zoster[f]				🟨 **2 doses RZV (preferred)**	🟨
Measles-mumps-rubella[g]	🟨 **1 or 2 doses depending on indication (if born in 1957 or later)**	🟨	🟨	🟨	
Pneumococcal 13-valent conjugate[h]	🟪	🟪	🟪	🟪	🟨 **1 dose**
Pneumococcal 23-valent polysaccharide[h]	🟪 **1 or 2 doses depending on indication**	🟪	🟪	🟪	🟨 **1 dose**
Meningococcal B[i]	🟪 **1 or more doses**	🟪	🟪	🟪	🟪
Hepatitis A[j]	🟪 **2 or 3 doses depending on vaccine**	🟪	🟪	🟪	🟪
Hepatitis B[k]	🟪 **3 doses**	🟪	🟪	🟪	🟪
Haemophilus influenzae type b[l]	🟪 **1 or 3 doses depending on indication**	🟪	🟪	🟪	🟪

🟨 Recommended for adults who meet the age requirement, do not have documentation of vaccination, or do not have evidence of past infection

🟪 Recommended for adults with an additional risk factor or another indication

☐ No recommendation

Figure 36.2. *Recommended Immunization Schedule for Adults—United States, 2019. Instructions for special situations and further details are published at http://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html. RZV indicates zoster vaccine, recombinant; Td, tetanus and diphtheria toxoids; Tdap, tetanus and diphtheria toxoids and acellular pertussis vaccine.*

[a] *Influenza inactivated or recombinant: 1 dose appropriate for age and health status annually.*

[b] *Previously did not receive Tdap at or after age 11 years, then 1 dose Tdap followed by Td booster every 10 years.*

[c] *No evidence of immunity to varicella: 2-dose series 4 to 8 weeks apart if previously did not receive varicella-containing vaccine. If previously received 1 dose of varicella-containing vaccine: 1 dose at least 4 weeks after first dose. Evidence of immunity: US-born before 1980 (except for pregnant women and health care personnel [which are special situations]), documentation of 2 doses varicella-containing vaccine at least 4 weeks apart, diagnosis or verification of history of varicella or herpes zoster by a health care provider, laboratory evidence of immunity or disease.*

[d] *Through age 26 years: 2- or 3-dose series human papillomavirus (HPV) vaccine depending on age at initial vaccination. Age ≥15 years at initial vaccination: 3-dose series HPV vaccine at 0, 1 to 2, and 6 months (minimum intervals: 4 weeks between doses 1 and 2, 12 weeks between doses 2 and 3, 5 months between doses 1 and 3; repeat dose if administered too soon). Age 9 through 14 years at initial vaccination and received 1 dose, or 2 doses less than 5 months apart: 1 dose HPV vaccine. Age 9 through 14 years at initial vaccination and received 2 doses at least 5 months apart: HPV vaccination complete, no additional dose needed. If completed valid vaccination series with any HPV vaccine, no additional doses needed.*

[e] *Through age 21 years: 2- or 3-dose series HPV vaccine depending on age at initial vaccination; age 22 through 26 years, may be vaccinated on the basis of individual clinical decision. Age ≥15 years at initial vaccination: 3-dose series HPV vaccine at 0, 1 to 2, and 6 months (minimum intervals: 4 weeks between doses 1 and 2, 12 weeks between doses 2 and 3, 5 months between doses 1 and 3; repeat dose if administered too soon). Age 9 through 14 years at initial vaccination and received 1 dose, or 2 doses less than 5 months apart: 1 dose HPV vaccine. Age 9 through 14 years at initial vaccination and received 2 doses at least 5 months apart: HPV vaccination complete, no additional dose needed. If completed valid vaccination series with any HPV vaccine, no additional doses needed.*

[f] *Age ≥50 years: 2-dose series RZV 2 to 6 months apart (minimum interval: 4 weeks; repeat dose if administered too soon) regardless of previous herpes zoster or previous zoster vaccine live (ZVL) (administer RZV at least 2 months after ZVL). Age ≥60 years: 2-dose series RZV 2 to 6 months apart (minimum interval: 4 weeks; repeat dose if administered too soon) or 1 dose ZVL if not previously vaccinated (if previously received ZVL, administer RZV at least 2 months after ZVL); RZV preferred over ZVL.*

A single dose of Tdap vaccine is recommended for all adults who have not received the Tdap vaccine, regardless of when they last received a tetanus-containing vaccine. A Td booster should be administered every 10 years thereafter.

Women of childbearing age should receive a dose of Tdap vaccine during each pregnancy, preferably between 27 and 36 weeks' gestation, regardless of the timing of previous Tdap or Td vaccination.

Recommendations for tetanus vaccination after an injury involve 3 possible steps.

1. If the 3-dose primary vaccination series is complete and the wound is clean and minor, no further vaccination is needed.
2. If the primary vaccination series is complete and the wound is contaminated, Td booster should be given if more than 5 years since the last booster.
3. If the primary vaccination status is unknown or incomplete, both Td and tetanus immune globulin should be given.

Varicella Vaccination

Evidence of immunity to varicella includes laboratory evidence of immunity or confirmation of disease, birth in the United States before 1980 (not considered evidence of immunity for health care workers or pregnant women), or the diagnosis or verification of a history of varicella or herpes zoster by a health care provider.

Healthy persons without evidence of immunity should receive varicella vaccination. Two doses should be given 4 to 8 weeks apart. If more than 8 weeks have passed since the first dose, the second dose can be given at any time.

Pregnant women without evidence of varicella immunity should be vaccinated in the immediate postpartum period. Women of childbearing age should wait 1 month to become pregnant after receiving the varicella vaccine.

HIV-positive adults with CD4 T-cell lymphocyte counts of 200 cells/μL or greater may receive 2 doses of vaccine 3 months apart.

Herpes Zoster Vaccination

All persons age 60 years and older should be vaccinated against herpes zoster (its eruptive rash is called *shingles*) unless a contraindication exists, such as severe immunodeficiency. The live zoster vaccine can be given regardless of a person's past history of varicella or zoster infection, although not during an active shingles episode. The US Food and Drug Administration has approved this vaccine for adults age 50 to 59 years.

In October 2017, the ACIP voted to recommend a new recombinant zoster vaccine for healthy adults age 50 years and older to prevent shingles and its related complications. The ACIP vote included the specification that the vaccine can be given to adults who previously received the then-current zoster vaccine. It is he preferred vaccine for those who have not been immunized previously.

MMR Vaccination

Adults born after 1956 who do not have a medical contraindication should receive the MMR vaccine if they do not have documentation of at least 1 MMR dose or an immune titer. Adults who have never been vaccinated should receive 2 doses given at least 1 month apart. If an unvaccinated person is exposed to measles, MMR vaccine should be given within 72 hours. Alternatively, immune globulin should be given within 6 days if the person is not a candidate for vaccination.

Rubella immunity should be documented for women of childbearing age. If a nonpregnant woman is not immune to rubella, she should be vaccinated. If a pregnant woman is not immune to rubella, she should be vaccinated in the immediate postpartum period.

A third dose of MMR vaccine can be considered for adults who have received a 2-dose series and have been identified as

Figure 36.2. *Continued*

[g] *No evidence of immunity to measles, mumps, or rubella, then 1 dose. Evidence of immunity: born before 1957 (except health care personnel) documentation of receipt of measles-mumps-rubella vaccine, laboratory evidence of immunity or disease (diagnosis of disease without laboratory confirmation is not evidence of immunity).*

[h] *Age ≥65 years (immunocompetent): 1 dose pneumococcal 13-valent conjugate (PCV13) if previously did not receive PCV13, followed by 1 dose pneumococcal 23-valent conjugate (PPSV23) at least 1 year after PCV13 and at least 5 years after last dose PPSV23. Previously received PPSV23 but not PCV13 at age ≥65 years: 1 dose PCV13 at least 1 year after PPSV23. When both PCV13 and PPSV23 are indicated, administer PCV13 first (PCV13 and PPSV23 should not be administered during same visit).*

[i] *Routine vaccination as shown.*

[j] *Not at risk but want protection from hepatitis A (identification of risk factor not required): 2-dose series hepatitis A or 3-dose series hepatitis A–hepatitis B.*

[k] *Not at risk but want protection from hepatitis B (identification of risk factor not required): 2- or 3-dose series hepatitis B or 3-dose series hepatitis A–hepatitis B.*

[l] *Routine vaccination as shown.*

(Modified from Centers for Disease Control and Prevention. Recommended immunization schedule for adults ages 19 years or older, United States, 2019 [Internet]. Atlanta [GA]; [cited 2019 Apr 24]. Available from https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf.)

at high risk during a mumps outbreak (https://www.cdc.gov/mmwr/volumes/67/wr/mm6701a7.htm).

Adults with HIV infection who have a documented CD4 lymphocyte count of 200 cells/μL or greater for at least 6 months and do not have evidence of measles, mumps, or rubella immunity should receive 2 doses of MMR vaccine at least 4 weeks apart.

Pneumococcal Vaccination

Two types of pneumococcal vaccines are available: pneumococcal conjugate vaccine (PCV13) with 13 pneumococcal subtypes and pneumococcal polysaccharide vaccine (PPSV23) with 23 subtypes.

Immunocompetent adults age 65 years and older should receive PCV13, followed by PPSV23 at least 12 months later.

Adults age 19 years and older who have immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leaks, or cochlear implants should also receive PCV13 first, followed by a dose of PPSV23 at least 8 weeks later (Table 36.2). PCV13 and PPSV23 should not be given together owing to increased risk of injection site reaction and the minimum acceptable interval of 8 weeks between the 2 vaccinations.

1. For persons previously vaccinated with PPSV23, PCV13 should be given at least 1 year after the most recent PPSV23 dose.
2. For those who require a second PPSV23 dose and have not received PCV13, the PCV13 vaccine should be given. The second PPSV23 dose should be given at least 8 weeks after PCV13 *and* at least 5 years after the most recent dose of PPSV23.

Adults age 19 years and older with chronic cardiovascular or pulmonary disease (including smokers and persons with asthma), diabetes mellitus, alcoholism, or chronic liver disease should receive a dose of PPSV23. They do not require revaccination after 5 years. At age 65 years, they should receive PCV13 followed by PPSV23 after 12 months.

HPV Vaccination

As of 2016, only the 9-valent HPV vaccine is available in the United States. Currently, no recommendations exist for revaccination with the 9-valent vaccine in individuals who have already completed the bivalent or quadrivalent vaccination series. Routine vaccination is recommended at age 11 or 12 years but can be started as early as age 9 years. If the first dose is given before a child's 15th birthday, the series can be completed with the second dose given at 6 to 12 months after the first. If the first dose is given on or after the 15th birthday, the series is completed with 2 additional doses, given at 1 to 2 months and at 6 months after the first dose with HPV9.

Vaccination also can be given from age 9 through 26 years for female patients and age 9 through 21 years for male patients. Men age 22 through 26 can also receive this vaccination if they have certain immunocompromising conditions; are gay or bisexual or are having sex with men; or are transgender persons who were not adequately vaccinated previously.

In autumn 2018, the US Food and Drug Administration approved the 9-valent HPV vaccine for patients age 27 through 45 years. However, the vaccine is not yet included in a recommended vaccination list by any guideline organization.

Although no evidence shows harm, the HPV vaccine is not recommended in pregnancy. Testing for pregnancy is not needed before administration of HPV vaccine. If pregnancy is detected after the initiation of vaccination series, further doses should be delayed until after gestation.

Meningococcal Vaccination

Four types of meningococcal vaccines are available, including 2 meningococcal conjugate vaccine against serogroups A,C,W and Y (MenACWY) and 2 serogroup B meningococcal vaccine (MenB). The MenB vaccine is available from 2 different manufacturers. Each manufacturer's vaccine has a different immunization schedule, and the 2 vaccines should not be interchanged.

All children 11 to 12 years old are vaccinated with the meningococcal conjugate vaccine, with a booster dose usually given around 16 years of age. The MenB vaccine may be given to persons age 16 through 23 years.

The meningococcal vaccines are indicated for adults with various risk factors (Table 36.2).

Hepatitis A Vaccination

Hepatitis A vaccination is recommended for certain populations only. Adults traveling to countries with intermediate to high rates of endemic hepatitis A virus infection should receive the vaccine. Vaccination is recommended for adults who are caring for an international adoptee from a country with intermediate to high rates of endemic hepatitis A virus infection, for receipt in the first 60 days of the adoptee's arrival to the United States. The vaccination should be given to persons with chronic liver disease, those receiving clotting factor concentrates, injection drug users, homeless individuals and men who have sex with men. Research personnel should be vaccinated if they work in a laboratory setting where hepatitis A exposure is a concern.

Hepatitis B Vaccination

Adult hepatitis B vaccination (a 3-dose series of initial dose, second dose at 1 month after initial dose, and third dose at 2 months after second dose) is recommended for high-risk groups. These populations include the following.

Table 36.2 • Medical Conditions or Other Indications for Administration of PCV13 and PPSV23 for Adults

		Immunization				
		PCV13 at Age ≥19 y	PPSV23[a] at Age 19-64 y		PCV13 at Age ≥65 y	PPSV23 at Age ≥65 y
Medical Indication	**Underlying Medical Condition**	**Recommended**	**Recommended**	**Revaccination**	**Recommended**	**Recommended**
None	None of those listed below				√	√ ≥1 y after PCV13
Immunocompetence	Alcoholism Chronic heart disease[b] Chronic liver disease Chronic lung disease[c] Cigarette smoking Diabetes mellitus		√		√	√ ≥1 y after PCV13 ≥5 y after any PPSV23 at age <65 y
	Cochlear implants CSF leaks	√	√ ≥8 wk after PCV13		√ If no previous PCV13 vaccination	√ ≥8 wk after PCV13 ≥5 y after any PPSV23 at age <65 y
Functional or anatomic asplenia	Congenital or acquired asplenia Sickle cell disease/other hemoglobinopathies	√	√ ≥8 wk after PCV13	√ ≥5 y after first dose of PPSV23	√ If no previous PCV13 vaccination	√ ≥8 wk after PCV13 ≥5 y after any PPSV23 at age <65 y
Immunocompromise	Chronic renal failure Congenital or acquired immunodeficiencies[d] Generalized malignancy HIV infection Hodgkin disease Iatrogenic immunosuppression[e] Leukemia Lymphoma Multiple myeloma Nephrotic syndrome Solid organ transplant	√	√ ≥8 wk after PCV13	√ ≥5 y after first dose of PPSV23	√ If no previous PCV13 vaccination	√ ≥8 wk after PCV13 ≥5 y after any PPSV23 at age <65 y

Abbreviations: CSF, cerebrospinal fluid; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

[a] This PPSV23 column only refers to adults age 19 through 64 years. All adults age 65 years and older should receive 1 dose of PPSV23 at 5 or more years after any prior dose of PPSV23, regardless of previous history of vaccination with pneumococcal vaccine. No additional doses of PPSV23 should be administered following the dose administered at age 65 years or older.

[b] Including congestive heart failure and cardiomyopathies.

[c] Including chronic obstructive pulmonary disease, emphysema, and asthma.

[d] Includes B- (humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease).

[e] Diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids and radiation therapy.

Modified from US Department of Health and Human Services. Pneumococcal vaccine timing for adults [Internet]. Atlanta [GA]; [cited 2019 Jan 18]. CDC updated 2015 Nov 30. Available from https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf.

1. Adults with high-risk behavior (persons with multiple sexual partners, persons with sexually transmitted diseases, men who have sex with men, and injection drug users)
2. Household and sexual contacts of persons with chronic hepatitis B virus infection
3. Health care personnel with exposure to blood or body fluids, or both
4. Adults with end-stage renal disease (including those receiving dialysis), chronic liver disease, or HIV infection and adults with diabetes mellitus who are younger than 60 years. Adults with diabetes who are 60 years of age or older can receive the vaccine at the discretion of their health care provider.
5. Travelers planning to stay in hepatitis B endemic areas
6. Adults (ie, persons who work, live, or receive care in the following settings: sexually transmitted disease treatment facilities, hemodialysis facilities, correctional facilities, and institutions for developmentally disabled persons

Haemophilus influenzae Type b Vaccination

Persons with asplenia or sickle cell disease should receive 1 dose of the *Haemophilus influenzae* type b (Hib) vaccine. Hib vaccination should be given 14 days or longer before elective splenectomy. A 3-dose regimen is recommended for recipients of hematopoietic stem cell transplants.

KEY FACTS

- ✓ Live virus vaccines are generally contraindicated—but inactivated vaccines are generally safe—for pregnant women and immunocompromised persons
- ✓ Tdap vaccination in pregnancy—a dose during each pregnancy, preferably between 27 and 36 weeks' gestation
- ✓ Herpes zoster vaccine—recommended for all persons age 60 years and older regardless of past history of varicella or zoster infection. The new recombinant vaccine is recommended for all persons older than 50 years.
- ✓ Pneumococcal vaccination recommendation for adults age 65 years and older—PCV13 vaccine followed in 6 to 12 months by PPSV23 vaccine
- ✓ Nine-valent HPV vaccine, recommended routinely at age 11 or 12 years, can also be given from age 9 through 26 years
- ✓ Hib vaccination before elective splenectomy—vaccine given at least 14 days before the operation

37 Quality Improvement and Patient Safety[a]

JORDAN M. KAUTZ, MD; JOHN C. MATULIS III, DO, MPH;
CHRISTOPHER M. WITTICH, MD, PharmD

Quality Improvement

Quality improvement, broadly interpreted, refers to any formal approach taken to understand and better the performance of a system. Quality improvement, conversationally, more often is taken to mean application of those methodologies or tools from industry to health care. The genesis of the quality movement in health care is often traced to 2 landmark Institute of Medicine reports. "To Err Is Human" cast a magnifying glass on safety gaps in the US care delivery, implicating preventable medical errors in the death of nearly 100,000 hospitalized patients annually. "Crossing the Quality Chasm" further indicted the entire care delivery system for failing its aim to provide consistent high-quality care to all people—care that is safe, timely, efficient, effective, equitable, and patient-centered. Both publications called for the redesign of health care systems to achieve and sustain improvements in patient outcomes.

In the system of profound knowledge, W. Edwards Deming described 4 components underpinning improvement: appreciation of a system, understanding of variation, theory of knowledge, and psychology. A basic appreciation of quality improvement methods and tools is now necessary for all physicians. Each physician has 2 jobs: to care for patients and to improve the systems through which that care is rendered.

Key Definition

Quality improvement: *systematic and continuous actions that lead to measurable improvement in health care services and the health status of targeted patient groups.*

Quality Improvement Methods

Many health care organizations today subscribe less to a single approach and more in favor of a blended framework. One is the Model for Improvement promoted by organizations such as the Institute for Healthcare Improvement. The model poses 3 questions: What are we trying to accomplish? How will we know that a change is an improvement? What changes can we make that will result in improvement? It then uses the PDSA (Plan, Do, Study, Act) cycle to test, refine, and spread the most promising change ideas. However, 3 approaches are singled out herein, for both their historical import and the fact that their respective emphases are germane to some of the most relevant and frequently encountered problems in health care.

Lean is a term first coined to describe the Toyota Production System during the early 1990s. The core idea is to maximize customer value while minimizing waste. Waiting is the most common waste that patients encounter. One example where Lean may be used is in operating rooms to improve turnover time between cases.

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[a] Recommended patient safety strategies previously published in Shekelle PG, Pronovost PJ, Wachter RM, McDonald KM, Schoelles K, Dy SM, et al. The top patient safety strategies that can be encouraged for adoption now. Ann Intern Med. 2013 Mar 5;158(5 Pt 2):365-8; used with permission.

Six Sigma is a set of tools and techniques developed by Motorola, Inc. The core idea is to remove defects and variation at the process level. The name refers to 6 standard deviations (SDs) around the mean, which represents 3.4 defects per 1 million opportunities. One example where Six Sigma may be used is in improvement of glycemic control in the intensive care unit.

Primary features of the PDSA method are use of iterative cycles, prediction-based testing of change, initial small-scale testing, and use of data over time to refine interventions.

Quality Improvement Tools

Important at the outset of any improvement effort is a well-conceived aim statement, which should specify the patient population affected, the health care problem addressed, a quantitative measure of the baseline level of performance, and a quantitative goal (how much) and explicit timeline (by when) for the improvement effort. Experience from other industries and of quality improvement experts indicates that applying some or all of the following tools, often regarded as foundational, can solve most operational problems.

Flowchart

Flowcharts are diagrams that use graphic symbols to depict the nature and flow of the steps in a process. Process maps can include diagrams such as a swimlane, a SIPOC (Suppliers, Inputs, Process, Outputs, Controls) diagram, or a value stream map (Figure 37.1).

Pareto Chart

The Pareto chart (Figure 37.2) is a specialized bar chart, showing potential contributors to quality gaps in descending order of frequency. The objective is to identify the vital few from the trivial many, elsewhere stated as *the 80-20 rule*: 80% of the problem is attributable to 20% of the causes.

Check Sheet

Check sheets are simple forms used to observe a process and to collect quantitative and qualitative data in real time. They should clearly articulate a data collection plan and the operational definitions. For example, they can be used to monitor adherence to hand hygiene or to strict isolation.

Histogram

Histograms are charts that group numeric data into bins, displaying the bins as segmented columns that depict the distribution of a data set, or how often values fall into ranges. Large data sets can be succinctly summarized graphically.

Key Definition

Histogram: *a chart that groups numeric data into bins and displays the bins as segmented columns, depicting the distribution of a data set.*

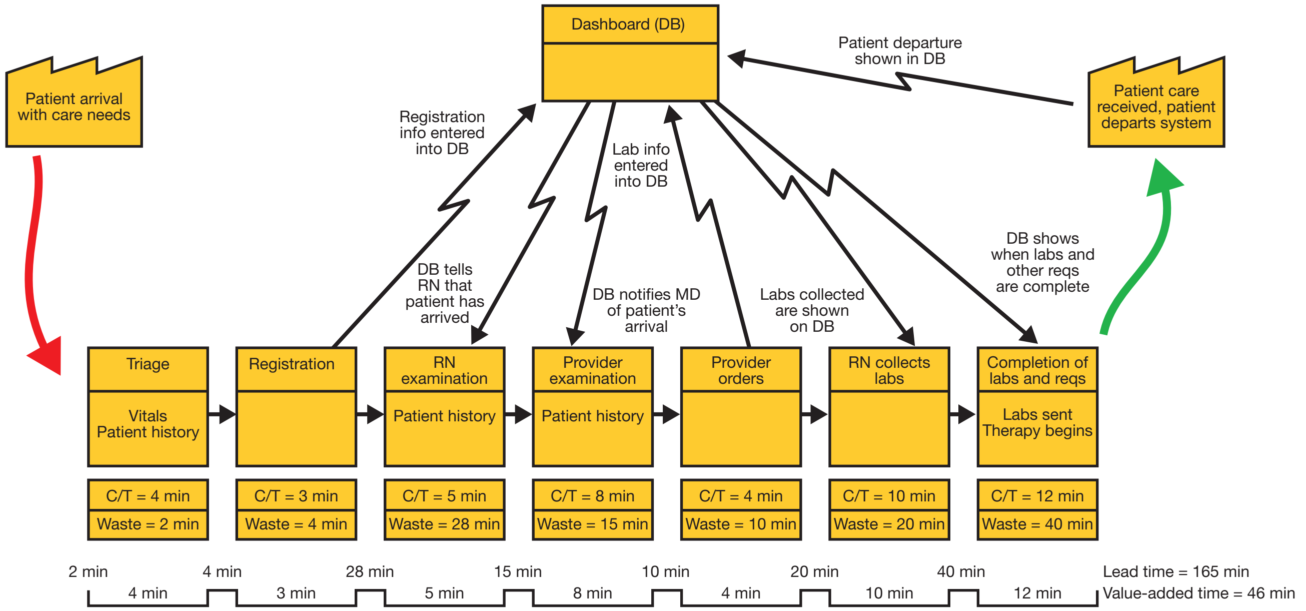
Dashboard (DB)
Patient arrival with care needs
Patient departure shown in DB
Patient care received, patient departs system
Registration info entered into DB
Lab info entered into DB
DB tells RN that patient has arrived
DB notifies MD of patient's arrival
Labs collected are shown on DB
DB shows when labs and other reqs are complete
Triage
Vitals Patient history
Registration
RN examination
Patient history
Provider examination
Patient history
Provider orders
RN collects labs
Completion of labs and reqs
Labs sent Therapy begins
C/T = 4 min
Waste = 2 min
C/T = 3 min
Waste = 4 min
C/T = 5 min
Waste = 28 min
C/T = 8 min
Waste = 15 min
C/T = 4 min
Waste = 10 min
C/T = 10 min
Waste = 20 min
C/T = 12 min
Waste = 40 min
2 min
4 min
28 min
15 min
10 min
20 min
40 min
4 min
3 min
5 min
8 min
4 min
10 min
12 min
Lead time = 165 min
Value-added time = 46 min

Figure 37.1. Value Stream Map. C/T indicates cycle time; info, information; lab, laboratory test result; MD, physician; reqs, requisitions; RN, registered nurse.

(From Dickson EW, Singh S, Cheung DS, Wyatt CC, Nugent AS. Application of Lean manufacturing techniques in the Emergency Department. J Emerg Med. 2009 Aug;37[2]:177-82. Epub 2008 Aug 23; used with permission.)

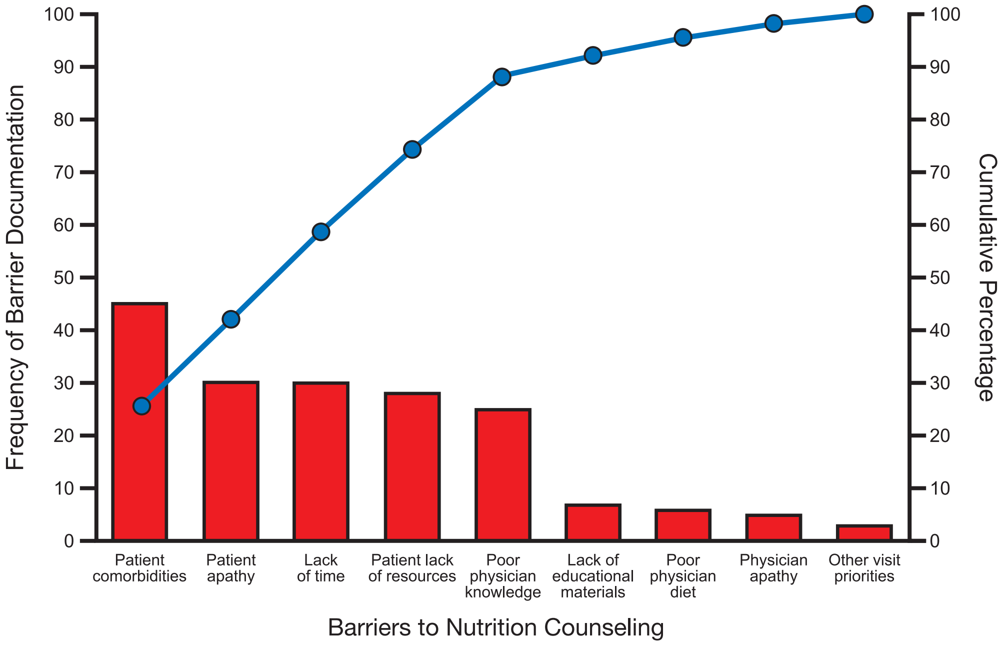

Figure 37.2. *Pareto Chart.*

(From Fluker SA, Whalen U, Schneider J, Cantey P, Bussey-Jones J, Brady D, et al. Incorporating performance improvement methods into a needs assessment: experience with a nutrition and exercise curriculum. J Gen Intern Med. 2010 Sep;25[Suppl 4]:S627-33; used with permission.)

Scatter Plot

Scatter plots are used to study and identify the possible relationship between 2 variables. The stronger the relationship, the more the diagram resembles a straight line. Correlation does not mean causation, because a confounder may influence both variables.

Cause-and-Effect Diagram

A cause-and-effect diagram (Figure 37.3) is a quality improvement tool that organizes root causes of a problem. These diagrams are also known as *fish bone diagrams* owing to their visual appearance or *Ishikawa diagrams* after the man who popularized their use.

Control Chart

Control charts (Figure 37.4), or statistical process control, are useful for understanding the performance of and changes in a process over time. The chart includes a line representing the mean in the center and lines called *control limits* on either side of the mean. The control limits show the variability of a process and are calculated from the underlying data. A point outside of the calculated control limits suggests a statistically significant

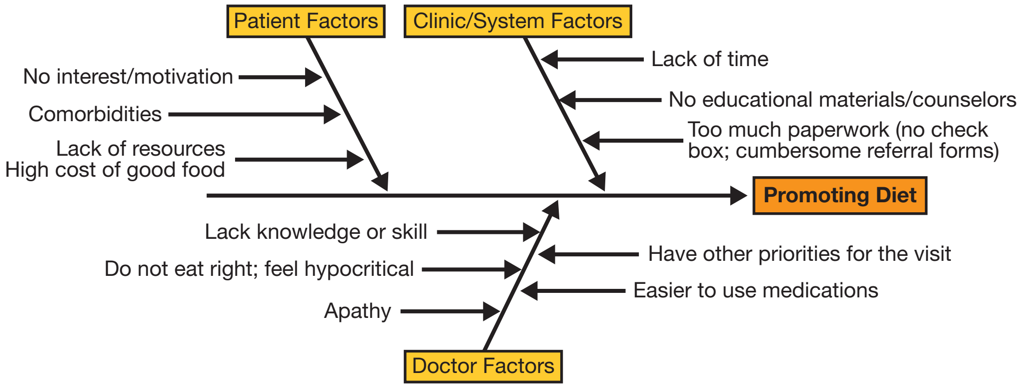
Patient Factors
Clinic/System Factors
No interest/motivation
Comorbidities
Lack of resources
High cost of good food
Lack of time
No educational materials/counselors
Too much paperwork (no check box; cumbersome referral forms)
Promoting Diet
Lack knowledge or skill
Do not eat right; feel hypocritical
Apathy
Have other priorities for the visit
Easier to use medications
Doctor Factors

Figure 37.3. *Cause-and-Effect (Fish Bone) Diagram.*

(From Fluker SA, Whalen U, Schneider J, Cantey P, Bussey-Jones J, Brady D, et al. Incorporating performance improvement methods into a needs assessment: experience with a nutrition and exercise curriculum. J Gen Intern Med 2010 Sep;25[Suppl 4]:S627-33; used with permission.)

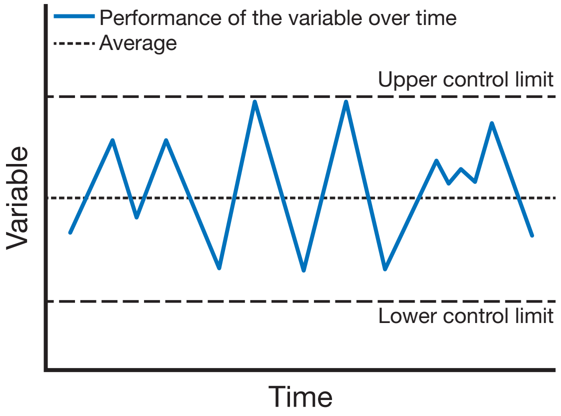

Figure 37.4. *Control Chart.*

(From Varkey P, Reller MK, Resar RK. Basics of quality improvement in health care. Mayo Clin Proc. 2007 Jun;82[6]:735-9; used with permission of Mayo Foundation for Medical Education and Research.)

change in underlying performance. The chart may include 2 additional lines—specification limits—that are dictated by customer requirements.

For example, an anticoagulation clinic may have a process by which, for a population, the mean international normalized ratio is 2.5 and 3.0 SDs plus or minus 1.1. The upper and lower control limits would be 3.6 and 1.4, respectively, but the upper and lower specification limits (in this case, the therapeutic window) would be 3.0 and 2.0, respectively.

A process is said to be stable when it is in statistical control, or when all data points lie within the calculated control limits. Numerous rules exist to analyze special cause variation. A different approach can be taken toward improvement depending on the type of variation in the process.

Patient Safety

Quality improvement and patient safety are complementary but not synonymous. Safety is but 1 dimension of quality care, and quality improvement but 1 behavior of safe care. First, "do no harm" is 1 of the fundamental precepts of biomedicine; if individuals do not intend harm, how does it nonetheless occur? James Reason proposed what has come to be known as the *Swiss Cheese Model*. Although successive layers of defense, barriers, and safeguards (*slice*) lie between causes and accidents, active failures and latent conditions (*holes*), if aligned, can and will result in harm. This perspective again places blame more squarely on the shoulders of the system, but it hardly exonerates the individual. Indeed, understanding of human factors—the interactions among humans and other elements of the system—is critical to improving safety by constructing systems wherein it is easier for persons to do the right thing and harder to do the wrong thing. Again, such an approach has been robustly used in other industries, including aviation and nuclear power. Such high-reliability organizations have the following characteristics: preoccupation with failure, commitment to resilience, and a just culture.

KEY FACTS

- ✓ Three quality improvement methods germane to health care—Lean, Six Sigma, and PDSA cycles
- ✓ Quality improvement tools—flowchart, Pareto chart, check sheet, histogram, scatter plot, cause-and-effect diagram, and control chart
- ✓ Check sheets—simple forms with such uses as monitoring adherence to hand hygiene or strict isolation
- ✓ Quality improvement and patient safety complement each other but are not the same
- ✓ Patient safety—can be improved with construction of systems that make it easier for individuals to do the right thing and harder to do the wrong thing

Box 37.1 • Patient Safety Strategies With Evidence Supporting Widespread Adoption and Implementation

Preoperative and anesthesia checklists to prevent operative and postoperative events

Bundles that include checklists to prevent central line–associated bloodstream infections

Interventions to reduce urinary catheter use, including catheter reminders, stop orders, or nurse-initiated removal protocols

Bundles that include head-of-bed elevation, sedation vacations, oral care, and subglottic suctioning endotracheal tubes to prevent ventilator-associated pneumonia

Hand hygiene

The do-not-use list for hazardous abbreviations

Multicomponent interventions to reduce pressure ulcers

Barrier precautions to prevent health care–associated infections

Use of real-time ultrasonography for central line placement

Interventions to improve prophylaxis for venous thromboembolism

Selected Topics

Recent scholarship has helped identify a broad array of patient safety strategies for which sufficient evidence exists in support of widespread adoption and implementation (Box 37.1).

Several major national safety initiatives target certain harmful events and call for increased efforts to eliminate the events. In addition to the initiatives just mentioned, emphasis has been placed on rapid response teams; evidence-based care for heart failure, myocardial infarction, and pneumonia; adverse drug events, including judicious use of high-risk medications (eg, anticoagulants, narcotics); errors related to handoffs and communication; and wrong-site surgical procedure.

38

Women's Health

NICOLE P. SANDHU, MD, PHD; CAROL L. KUHLE, DO, MPH

Menstruation and Menopause

Menstruation

The menstrual cycle is composed of the follicular (proliferative), periovulatory, and luteal (secretory) phases. At periovulation, the mature follicle triggers a surge in luteinizing hormone (LH) level, causing ovum release and stimulating the residual ovarian follicle to transform into a corpus luteum. Circulating estrogen and progestin levels increase. A thickened, enriched endometrium develops owing to progestin secretion from the corpus luteum. Without fertilization, the corpus luteum atrophies, estrogen and progestin levels decline, follicle-stimulating hormone (FSH) release is stimulated, and the endometrium sloughs (menstruation). FSH then initiates follicle maturation, increasing estrogen production and endometrial growth. The duration of menstruation averages 4 to 6 days. The average menstrual cycle lasts 24 to 35 days, but about 20% of women have irregular cycles. Women at extremes of body mass index often have longer mean cycle lengths. Women within 5 to 7 years after menarche and 10 years before menopause have greater cycle variability.

Premenstrual Syndrome

Premenstrual syndrome (PMS) is the cyclic occurrence of symptoms a week before menses that interfere with social and economic function and are relieved within a few days after menstruation. Symptoms include irritable mood, abdominal bloating, breast tenderness, back pain, headache, appetite changes, fatigue, and difficulty concentrating. Premenstrual dysphoric disorder (PDD) differs in that emotional symptoms predominate in severity over physical symptoms. PDD may include markedly depressed mood, anxiety, anger or emotional lability, lethargy, difficulty concentrating, insomnia or hypersomnia, and a sense of being out of control. Symptoms occur during the last week of the luteal phase and resolve within a few days of menstruation. To meet the diagnostic criteria for PDD, symptoms must markedly interfere with work, school, or usual social activities and relationships with others.

Reduction in caffeine, salt, sugar, and alcohol intake and consumption of small, frequent meals with complex carbohydrates may help some women with mild to moderate premenstrual symptoms and PMS. Exercise, stress reduction, and relaxation techniques can also be helpful, as can supplementation with calcium carbonate, vitamin $B_{6,}$ or magnesium. Nonsteroidal anti-inflammatory drugs (NSAIDs) and oral contraceptives are effective for physical symptoms of PMS. Selective serotonin reuptake inhibitors are the treatment of choice for emotional symptoms. They may be prescribed continuously or cyclically (luteal phase).

Abnormal Uterine Bleeding in Women of Reproductive Age

Bleeding that is excessive or outside the normal cyclic bleeding pattern is called *abnormal uterine bleeding* (Box 38.1). The terms *menorrhagia, metrorrhagia,* and *oligomenorrhea* have been replaced by *heavy menstrual bleeding* (ovulatory heavy bleeding), *intermenstrual bleeding* (bleeding in between regular menses), and *ovulatory dysfunction* (irregular nonovulatory bleeding).

Etiologic factors of uterine bleeding are classified with the mnemonic PALM COEIN. PALM (polyp, adenomyosis, leiomyoma, and malignancy and hyperplasia) represents structural

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The editors and authors acknowledge the contributions of Lynne T. Shuster, MD, and Amy T. Wang, MD, to the previous edition of this chapter.

Box 38.1 • Possible Causes of Abnormal Uterine Bleeding

- Pregnancy
- Anovulation or oligo-ovulation
- Fibroids
- Polyps, endometrial or endocervical
- Adenomyosis
- Endometriosis
- Infection, including PID
- Endometrial hyperplasia
- Endometrial carcinoma
- Coagulation disorders
- Hyperprolactinemia
- Liver disease
- Thyroid dysfunction
- Obesity
- Anorexia
- Rapid fluctuations in weight
- Corticosteroids
- Hormonal contraceptives
- Tamoxifen

Abbreviation: PID, pelvic inflammatory disease.

Box 38.2 • Assessment of Menstrual Bleeding Characteristics

- Patient history
  - Date of last menstrual period
  - Timing, duration, and amount of bleeding
  - Bleeding pattern
  - Associated pain
  - Evidence of ovulatory cycling (regular menses, cyclic symptoms)
  - Contraceptive history
  - Weight changes
  - Medications
  - Substance abuse
  - Effect of bleeding on quality of life
- Physical examination
  - Pelvic, breast, and thyroid examinations
  - Body habitus and hair distribution
    - Obesity
    - Underweight
    - Hirsutism
  - Mucosal lesions as cause of postcoital spotting or bleeding
    - Vaginal atrophy
    - Cervical lesions
  - Pregnancy, ectopic pregnancy
- Laboratory evaluation
  - Pregnancy testing
  - Complete blood cell count
  - Thyrotropin (thyroid-stimulating hormone) and prolactin (if ovulatory dysfunction)
  - Cervical cancer screening
  - Gonorrhea and chlamydial infection
  - Endometrium
  - Transvaginal ultrasonography

causes of bleeding; COEIN (coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified) represents nonstructural causes.

The history should identify patient characteristics, including date of last period and the timing, duration, and amount of bleeding (Box 38.2). History suggestive of an underlying bleeding disorder should be elicited, especially among adolescent girls. Physical examination is a central part of patient care for uterine bleeding. A uterine source of bleeding should be verified whenever possible. Obese women can have irregular, anovulatory bleeding due to increased circulating estrogen (from androgen conversion in adipose tissue). Underweight women may have ovulatory dysfunction as a result of hypothalamic dysfunction. Hirsutism suggests polycystic ovary syndrome.

Laboratory assessment should be performed as appropriate (Box 38.2). Testing for gonorrhea and chlamydial infection should be done for patients who are at high risk, have purulent discharge, or have tenderness on pelvic examination. For women age 45 years or older, endometrial sampling is recommended as first-line testing. For women younger than 45 years, endometrial cancer is related to proliferation in the absence of endometrial withdrawal bleeding. Thus, endometrial sampling is indicated for women age 45 years or older who have persistent anovulation, do not respond to medical therapy, or are at high risk for endometrial cancer. Transvaginal ultrasonography is useful to evaluate for structural abnormalities suspected from the physical examination and for continued symptoms despite treatment. Transvaginal ultrasonography to measure endometrial thickness can be an alternative to endometrial sampling for postmenopausal women but not premenopausal women, because endometrial thickness varies through the menstrual cycle.

When possible, treatment is directed at the underlying cause, including medical conditions (eg, polycystic ovarian syndrome, hypothyroidism, hyperprolactinemia, chronic endometritis) and structural abnormalities (eg, endometrial polyps, submucosal fibroids). Structural irregularities can be resected with hysteroscopy. Pharmacologic therapy can be given to control bleeding and restore quality of life. Estrogen-progestin contraceptives, oral progestin, and a levonorgestrel-releasing intrauterine device (IUD) are effective first-line therapies for these abnormalities. NSAIDs and tranexamic acid can be used if contraindications to hormonal therapies exist. For women who are trying to conceive in the near future, oral progestin is preferred; NSAIDs also can be used but should be stopped at conception because of increased risk of congenital anomalies and miscarriage. Definitive therapy with endometrial ablation or hysterectomy is an option for women who have completed childbearing and want to avoid medication or an IUD.

KEY FACTS

- ✓ Emotional symptoms predominate in premenstrual dysphoric disorder; physical symptoms in PMS
- ✓ NSAIDs and oral contraceptives are effective for physical symptoms of PMS; selective serotonin reuptake inhibitors for emotional symptoms
- ✓ PALM COEIN mnemonic for abnormal uterine bleeding—PALM (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia) represents structural causes; COEIN (coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified) represents nonstructural causes
- ✓ Endometrial sampling is needed to evaluate abnormal uterine bleeding in women age 45 years or older
- ✓ First-line therapies for abnormal uterine bleeding—estrogen-progestin contraceptives, oral progestin, or levonorgestrel-releasing intrauterine device

Contraception and Infertility

Contraception

Contraceptive methods include hormonal, barrier, chemical, and physiologic approaches. None are 100% effective, and all carry some degree of risk (Table 38.1).

Contraception factors that need consideration include efficacy, convenience, duration of action, reversibility and time to return of fertility, effect on uterine bleeding, affordability, and protection against sexually transmitted infections. The balance of advantages and disadvantages of each method guides individual decisions. Methods consistent with a woman's values and lifestyle are the most likely to be successful. Effective contraceptive use requires education and counseling about appropriate use.

Table 38.1 • Contraception Options

Contraceptive Method	Adverse Effects/Risks	Benefits
Combined hormonal contraceptives (pill, patch, vaginal ring)	Increased risk of DVT, MI, CVA, HTN, hepatic adenoma; nausea, headaches, spotting, mastalgia, mood changes	Reduced risk of dysmenorrhea, heavy menstrual bleeding, anemia, ovarian and endometrial cancers, acne
Progestin-only pill	Unpredictable spotting, bleeding	Can use when estrogen is contraindicated (HTN, CVD, clotting) Does not interfere with lactation
Depo-progestin	Menstrual changes, weight gain, headache, delayed return to ovulation	Lactation not disturbed; convenience
Progesterone implant	Delayed return to ovulation	Convenience
IUD (copper or levonorgestrel)	Spotting, cramping, back pain	Convenience
Condom	Requires planning ahead; may decrease sensation	Protects against STIs
Diaphragm	Requires planning ahead; must be left in place for 6-8 h after sexual intercourse; requires spermicide	Avoids hormone-related adverse effects
Female sterilization (tubal ligation)	Surgical complications, increased risk of ectopic pregnancy, regret	Convenience
Male sterilization (vasectomy)	Surgical complications	More effective and fewer complications than female sterilization
Fertility awareness–based methods	Pregnancy risk 9%-19%; takes time to learn; requires abstaining from sexual intercourse or using barrier method during fertile window	Learning biomarkers of fertility can help a committed couple plan pregnancy or avoid pregnancy

Abbreviations: CVD, cardiovascular disease; CVA, cerebrovascular accident; DVT, deep vein thrombosis; HTN, hypertension; IUD, intrauterine device; MI, myocardial infarction; STI, sexually transmitted infection.

The most common form of hormonal contraceptives is the combination estrogen-progestogen pill. Estrogen prevents ovulation through suppression of FSH and LH and contribution to corpus luteum degeneration. Progestogens inhibit ovulation through suppression of midcycle LH and FSH peak. They also thicken cervical mucus, alter tubal motility, and lead to an atrophic endometrium, thereby interfering with sperm transport and fertilized ovum implantation.

Combination estrogen-progestogen pills are highly effective (97%-99%) when used ***correctly***; the failure rate is about 3 per 1,000 in the first year of use. However, with ***typical*** use, the failure rate is estimated to be 8%. Noncontraceptive benefits include menstrual cycle regularity; maintenance of bone mineral density; reduced risk of endometrial and ovarian cancer; and, with frequent use, the treatment of acne, hirsutism, symptomatic leiomyomas, and endometriosis. Common adverse effects include breakthrough bleeding (more common with missed pills or low-dose estrogen), bloating, and breast tenderness. Some contraindications to the use of estrogen-containing oral contraceptives do exist (Box 38.3). Progestogen-only pills should be considered for women with migraine headaches, hypertension, diabetes mellitus, personal or family history of thromboembolism, cardiac or cerebrovascular disease, or hypertriglyceridemia and for women older than 35 years who smoke.

KEY FACTS

- ✓ As typically used, combination oral contraceptives fail in approximately 8% of patients
- ✓ Noncontraceptive benefits of oral contraceptives—menstrual cycle regularity, maintenance of bone mineral density, reduced risk of endometrial and ovarian cancer, and treatment of other conditions
- ✓ Common adverse effects of oral contraceptives—breakthrough bleeding, bloating, and breast tenderness
- ✓ Consider progestogen-only pills for women smokers older than 35 years

Box 38.3 • Contraindications to Use of Estrogen-Containing Oral Contraceptives

- Absolute contraindications
  - History of DVT or PE, unless a defined nonhormonal cause
  - History of arterial thromboembolism
  - Active liver disease
  - Cardiovascular disease (eg, CHF, myocardial infarction or CAD, atrial fibrillation, mitral stenosis, mechanical heart valve)
  - Systemic diseases that affect vascular system (eg, SLE, diabetes mellitus with retinopathy or nephropathy)
  - Cigarette smoking by women age >35 y
  - Uncontrolled hypertension
  - History of breast cancer
  - Undiagnosed amenorrhea
- Relative contraindications
  - Classic migraine
  - Hypertriglyceridemia
  - Depression

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; DVT, deep vein thrombosis; PE, pulmonary embolism; SLE, systemic lupus erythematosus.

Women seeking longer-acting contraception also have several options. Depot medroxyprogesterone acetate injections can be given either intramuscularly or subcutaneously every 3 months. Several forms of long-acting progestin-only contraception are available as implants in the upper arm (etonogestrel and levonorgestrel) or as an IUD; these last for 3 to 5 years depending on type and formulation. Copper IUDs are another option for women who have contraindications to hormone use. They can be left in place for 10 years.

Infertility

Infertility is the inability to conceive after 1 year of intercourse without contraception. It can be due to male or female factors, or both. Its cause may be difficult to identify. Declining oocyte quality with advanced age is a major cause of infertility. Other common causes of female infertility are ovulatory disorders (eg, polycystic ovary syndrome, hypothyroidism, hyperprolactinemia, eating disorders, extreme stress), endometriosis, pelvic adhesions, and tubal abnormalities.

Key Definition

Infertility: *the inability to conceive after 1 year of intercourse without contraception; may be due to male or female factors, or both.*

Evaluation includes the patient's history (eg, duration of infertility; prior evaluation or interventions; menstrual history; sexual history; lifestyle factors, including exercise, diet, stress, smoking, and substance abuse; medical and surgical history). It also involves partner semen analysis, documentation of ovulation through history and midluteal serum progesterone level, assessment of ovarian reserve (day 3 serum FSH and estradiol levels), and assessment of the fallopian tube patency and the uterus with hysterosalpingography. Endocrinologic causes can be excluded through measurement of prolactin and thyroid function.

Medical Issues of Pregnancy

Preconception Counseling and Prenatal Care

Prenatal care is associated with improved pregnancy outcomes. Lifestyle factors—diet, exercise, and avoidance of tobacco, alcohol, and illicit drug use—should be addressed. Adequate folic acid supplementation before conception decreases the risk of neural tube defects. Alcohol use during pregnancy is associated with early spontaneous abortion, placental abruption, and fetal alcohol syndrome and is the third leading cause of intellectual disability in infants. Smoking is associated with low birth weight, perinatal infant death, infertility, spontaneous abortion, ectopic pregnancy, placenta previa and placental abruption, and sudden infant death syndrome. Caffeine intake of 1 to 2 cups of coffee or other caffeinated beverage daily is not associated with miscarriage or birth defects.

Immunizations and Pregnancy

Live vaccines should be avoided during pregnancy. However, certain inactivated vaccines should be routinely administered during pregnancy. These include the inactivated influenza vaccine during influenza season and the tetanus-diphtheria-acellular pertussis (Tdap) vaccine, which is recommended for all pregnant women during 27 to 36 weeks' gestation for each pregnancy (Table 38.2).

Medical Care During Pregnancy

Hypertension complicates up to 10% of pregnancies and is an important cause of maternal and fetal morbidity and death.

Table 38.2 • Vaccinations and Pregnancy

Vaccination	Consideration
Inactivated	
Hepatitis A	Vaccinate if at high risk
Hepatitis B	Vaccinate if at risk
Human papillomavirus	Not recommended during pregnancy Before or after pregnancy, vaccinate through age 26 y
Influenza	Vaccinate with inactivated vaccine all women who will be pregnant during influenza season *Avoid administration of nasal flu vaccine, a live attenuated viral vaccine, during pregnancy*
Meningococcus	Administer if indicated Administered to women at increased risk (eg, those with asplenia due to terminal complement component deficiencies, first-year college students living in a dormitory, military recruits, travelers to countries where meningococcal disease is hyperendemic
Pneumococcus	Administer if indicated Administer to women at increased risk (eg, those with asplenia, diabetes mellitus, cardiopulmonary disease, CKD, or CLD)
Toxoid	
Tdap	Administer during each pregnancy, ideally between 27 and 36 wk of gestation If missed, administer in immediate postpartum period
Live attenuated vaccines	Avoid during pregnancy
Influenza nasal vaccine	Avoid during pregnancy
MMR	Avoid conception for 4 wk after MMR vaccination
Varicella	Avoid conception for 4 wk after varicella vaccination

Abbreviations: CKD, chronic kidney disease; CLD, chronic liver disease; MMR, measles, mumps, and rubella; Tdap, tetanus-diphtheria-acellular pertussis.

Pregnancy creates a thrombogenic state, yet thromboembolism is uncommon during pregnancy. However, women with hereditary thrombophilias are at high risk for thrombosis during pregnancy, with potentially serious complications. Low-molecular-weight heparin is the preferred treatment of thromboembolism during pregnancy or is given for prevention in high-risk women. Warfarin is teratogenic and increases the risk of spontaneous abortion; it should be avoided during pregnancy.

Maternal hypothyroidism is associated with infertility, miscarriage, stillbirth, placental abruption, preeclampsia, and motor and intellectual disability in the infant. Thyrotropin (thyroid-stimulating hormone) should be measured early in pregnancy, and women taking thyroid hormone should be monitored regularly. About 20% require a dose increase. Hyperthyroidism occurs in only about 0.2% of pregnancies. Symptoms and signs may overlap with normal findings in pregnancy, and low weight gain may be the only clue. Poorly controlled hyperthyroidism may lead to spontaneous abortion, premature delivery, preeclampsia, congestive heart failure, and low birth weight. To prevent fetal goiter and hypothyroidism, maternal hyperthyroidism must be treated. Propylthiouracil is the treatment of choice during the first trimester of pregnancy (to avoid potential teratogenic effects of methimazole), whereas methimazole is recommended after the first trimester to avoid propylthiouracil-associated liver damage. For many women, the dose of medication can be tapered or discontinued in the last trimester. Radioiodine is absolutely contraindicated during pregnancy and lactation. Surgery should not be considered unless hyperthyroidism is refractory to medical therapy.

Diseases of the Uterus and Adnexa

Endometriosis

Endometriosis is the presence of endometrial glands and stroma outside the endometrial cavity and uterine wall. The most common sites (in decreasing frequency) are the ovaries, cul-de-sac, broad and uterosacral ligaments, uterus, fallopian tubes, sigmoid colon, appendix, and round ligaments. The most common symptom is pain, which may manifest as pelvic pain, chronic dyspareunia or dysmenorrhea, or cyclic bowel or bladder symptoms. Endometriosis is found in 20% to 40% of infertile women and in up to 65% of women with chronic pelvic pain. Physical examination findings may be normal. Localized tenderness in the cul-de-sac or uterosacral ligaments suggests endometriosis. Pelvic ultrasonography findings may be suggestive of the diagnosis, but definitive diagnosis requires direct visualization and biopsy of endometriosis, ideally laparoscopically.

Key Definition

Endometriosis: *the presence of endometrial glands and stroma outside the endometrial cavity and uterine wall.*

Table 38.3 • Treatment Options for Endometriosis

Symptom	Treatment Options	Impact on Endometriotic Implants	Adverse Effects
Mild pelvic pain	Analgesics (eg, NSAIDs)	Do not reduce size	Minimal
	Oral contraceptives	Evidence conflicts on whether therapy reduces size or inhibits progression of disease	Minimal
Moderate to severe pain Pain that does not respond to analgesics or oral contraceptives	GnRH agonist (eg, leuprolide, nafarelin, goserelin)	Reduces size	Menopausal symptoms, bone loss FDA approval for no more than 6 mo of continuous use Combination with progestins or low-dose estrogen-progestin therapy minimizes adverse effects and allows prolonged use
	Progestins (oral or depot medroxyprogesterone acetate)	Evidence unclear as to effect on size or inhibition of disease progression	Weight gain, irregular uterine bleeding, mood changes
	Danazol	Reduces size	Weight gain, muscle cramps, decreased breast size, acne, hirsutism, lipid changes, hot flushes, mood changes
Severe pain Pain unresponsive to medical management Advanced disease Large or symptomatic endometrioma	Surgery	Reduces size of implants and endometriotic adhesions	May lead to development of postsurgical adhesions

Abbreviations: FDA, US Food and Drug Administration; GnRH, gonadotropin-releasing hormone; NSAID, nonsteroidal anti-inflammatory drug.

Treatment is directed at symptom relief (Table 38.3) and depends on symptom severity, disease extent and location, desire for pregnancy, patient age, and prior treatment response. Empirical medical therapy with an NSAID, oral contraceptive, or gonadotropin-releasing hormone agonist is reasonable when endometriosis is suspected before a definitive surgical diagnosis. If this fails, a diagnostic laparoscopy is often done, during which ablation and excision of implants and adhesions can be performed. Postoperative medical hormone-suppressive therapy has been shown to decrease recurrence. Definitive surgical therapy involves hysterectomy and oophorectomy. The surgical approach depends on the severity of symptoms, the age of the patient, and the desire for fertility.

KEY FACTS

- ✓ Tdap vaccine is recommended at 27 to 36 weeks' gestation during each pregnancy
- ✓ The treatment of choice for hyperthyroidism during pregnancy is propylthiouracil
- ✓ Endometriosis most commonly causes pain, manifested as pelvic pain, chronic dyspareunia or dysmenorrhea, or cyclic bowel or bladder symptoms
- ✓ Factors to consider in choosing the treatment of endometriosis—symptom severity, disease extent and location, desire for pregnancy, patient age

Uterine Fibroids

Uterine leiomyomas (fibroids or myomas) are benign monoclonal tumors that arise from the smooth muscle of the myometrium. They are the most common female pelvic tumors, occurring in 50% to 80% of women, and are most prevalent during the reproductive years, usually regressing after menopause. Approximately 25% are symptomatic. Fibroid-related symptoms are grouped into 3 categories: menstrual (eg, dysmenorrhea, heavy menstrual bleeding), bulk-related (eg, pelvic pain, pelvic pressure, urinary frequency, constipation, dyspareunia), and reproductive dysfunction (eg, recurrent miscarriage, obstetric complications).

Key Definition

Uterine leiomyomas (fibroids or myomas): *benign monoclonal tumors that arise from the smooth muscle of the myometrium.*

Fibroids are suggested by an enlarged, irregularly shaped, firm, nontender uterus on pelvic examination. Transvaginal ultrasonography should be done if the diagnosis is uncertain; fibroids appear as symmetrical, well-defined, hypoechoic, heterogeneous masses. Hysteroscopy may be used, particularly if myomectomy is planned. Annual pelvic examination should be done; further evaluation is warranted if symptoms change or uterine size increases. Routine surveillance imaging is not recommended.

Treatment is necessary only if fibroids are symptomatic. A trial of medical therapy before surgical therapy is appropriate for symptomatic fibroids (anemia, heavy bleeding, or pain). Gonadotropin-releasing hormone agonists (eg, leuprolide) cause amenorrhea and reduce uterine size in most cases. The levonorgestrel IUD may reduce menstrual blood loss and uterine size. Surgical treatment is indicated when symptoms persist despite medical treatment, when infertility or recurrent pregnancy loss is related to fibroids, or when malignancy is suspected. Surgery should be considered in a postmenopausal woman with a new or enlarging pelvic mass to exclude uterine sarcoma.

Surgical options include myomectomy (if there is no suspicion of malignancy) or hysterectomy. Myomectomy involves removal of the fibroids with uterine conservation and preserves childbearing potential. Less invasive options when childbearing is complete and there is no suspicion of malignancy include endometrial ablation, myolysis, uterine artery embolization, and magnetic resonance–guided focused ultrasound ablation.

Cervical Cancer Screening

Cervical cancer screening is covered in Chapter 36, "Preventive Medicine." Additional evaluation and treatment based on cervical cytologic findings depend on the abnormality. Up-to-date consensus guidelines and algorithms for managing abnormal results of cervical cancer screening tests can be found online through the American Society of Colposcopy and Cervical Pathology.

Box 38.4 • Conditions Commonly Associated With Vulvar Itching

Acute

Infections

- Fungal, including candidiasis and tinea cruris
- Trichomoniasis
- Vulvovaginal candidiasis
- Molluscum contagiosum
- Infestations, including scabies and pediculosis

Contact dermatitis (allergic or irritant)

Chronic

Dermatoses

- Atopic and contact dermatitis
- Lichen sclerosus, lichen planus, lichen simplex chronicus
- Psoriasis
- Genital atrophy

Neoplasia

- Vulvar intraepithelial neoplasia, vulvar cancer
- Paget disease

Vulvar manifestations of systemic disease

- Crohn disease

From ACOG Practice Bulletin No. 93: diagnosis and management of vulvar skin disorders. Obstet Gynecol. 2008 May;111(5):1243-53; used with permission.

Vulvar Skin Disorders

Vulvar itching, burning, and pain are common symptoms and may be acute or chronic. Common causes of vulvar pruritus (Box 38.4) include vulvovaginal candidiasis, contact dermatitis, lichen sclerosus, neoplastic conditions (eg, squamous cell carcinoma, Paget disease of the vulva), or vulvar manifestations of systemic disease. Vulvodynia is pain at the vaginal opening often described as burning, stinging, rawness, or soreness, with or without pruritus. Typically, the vulvar skin changes are not visible, and cotton swab testing reproduces pain. Contact dermatitis may be acute (blisters, itching, and weeping) or chronic (redness, burning, and swelling). Physical findings range from mild erythema and scaling to intense erythema, fissures, erosions, and ulcers. Treatment is removal of the offending irritant or allergen and topical corticosteroid ointments.

Lichen simplex chronicus may present with persistent intense itching, typically with scaling and lichenified plaques that result from long-term rubbing or scratching. If it is a long-standing condition, vulvar skin may appear thickened and leathery, with areas of hyperpigmentation or hypopigmentation.

Lichen sclerosus has the following features: thinned, whitened, and crinkling skin; porcelain-white papules and plaques; areas of ecchymoses or purpura; and possible agglutination of tissues with fusion of the labia minora and phimosis of the clitoral hood. Biopsy should be done to confirm the diagnosis before initiation of topical corticosteroid treatment (typically clobetasol) and to rule out squamous cell carcinoma.

Lichen planus is an inflammatory disorder with mucous membrane findings ranging from white irregular lines to deep, painful, erythematous erosions and scarring resulting in vaginal obliteration. As with lichen sclerosus, biopsy is recommended to confirm the diagnosis and rule out cancer. Treatment options include topical and systemic corticosteroid, topical and oral cyclosporine, topical tacrolimus, and intramuscular triamcinolone. Lichen planus is chronic and tends to be treatment resistant.

The common symptoms of vulvovaginal atrophy are vulvar irritation and dryness. On examination, loss of labial and vulvar fullness is seen, with urethral and vaginal mucosal pallor and dryness. Diagnosis is based on physical examination findings and is confirmed by an increased vaginal pH (6.0-7.5). Treatment is with topical estrogen (cream, tablet, or vaginal ring).

Perimenopause

Perimenopause typically lasts several years and is characterized by erratic hormone levels and irregular menstrual periods. Symptoms such as hot flushes, vaginal dryness, and sleep disturbances are common, as are anovulatory cycles, which contribute to irregular menstrual bleeding. Despite reduced fertility, pregnancy is possible until menopause (either 12 months of no menstrual periods or FSH levels consistently >30 mIU/mL).

Menstrual changes may include lighter or heavier bleeding, irregular bleeding duration, or skipped periods. Certain bleeding patterns warrant evaluation: very heavy flow, especially with clots; bleeding lasting more than 7 days; bleeding intervals less than 21 days; intermenstrual spotting or bleeding; and postcoital bleeding.

The decision about when to stop oral contraceptives or switch to postmenopausal hormone therapy is not straightforward. Clinical signs of menopause are masked by use of hormonal contraceptives. FSH levels are labile in perimenopause, and unless they are consistently higher than 30 mIU/mL, menopause is not confirmed. Hormonal contraceptives may lower FSH levels, confounding interpretation. FSH testing 7 to 14 days after last use of oral contraceptives, while alternative contraception is being used, can help to establish menopause, if needed.

Terms related to menopause are defined in Box 38.5.

Menopause

Menopause is the permanent cessation of menses occurring when ovarian follicles are depleted. Natural menopause, a clinical diagnosis, is confirmed when a woman has no menses for 12 months, typically occurring between ages 42 and 58 years (average, 51 years). It often occurs earlier in smokers and nulliparous women. Menopause also may be induced by surgery, chemotherapy, or pelvic irradiation.

Box 38.5 • Menopause-Related Terms

Natural/spontaneous menopause: the final menstrual period, confirmed after 12 consecutive mo of amenorrhea with no obvious pathologic cause

Induced menopause: permanent cessation of menstruation after bilateral oophorectomy or iatrogenic ablation of ovarian function

Perimenopause or menopausal transition: span of time when menstrual cycle changes and endocrine changes occur a few years before and 12 mo after the final menstrual period, resulting from natural menopause

Premature menopause: menopause reached at or before age 40 y

Premature ovarian failure: ovarian insufficiency occurring before age 40 y and leading to permanent or transient amenorrhea

Early menopause: natural or induced menopause occurring at or before age 45 y

The hallmark symptom of menopause is hot flushes (also called *hot flashes*) (abrupt onset of warmth and red skin blotching involving the chest, face, and neck), often associated with transient anxiety, palpitations, and profuse sweating. Most menopausal women have hot flashes; 10% to 15% report that they are frequent or severe. Hot flashes often begin more than 2 years before menopause and usually peak within 2 to 3 years after menopause, but they continue in some women for many years after menopause. Frequency, duration, and intensity vary. Hot flashes coincide with declining estrogen levels, but they are not due to hypoestrogenism. The mechanism is attributed to dysfunction of the thermoregulatory center in the hypothalamus.

Other postmenopausal symptoms include vaginal dryness and irritation, urinary urgency and frequency, dyspareunia, changes in sexual function, mood swings, and cognitive function changes. Menopausal symptoms tend to be more intense after surgically induced menopause than natural menopause.

When hot flashes occur in a healthy woman of typical menopausal age, no diagnostic testing is necessary. However, if the clinical scenario is atypical, testing for an increased FSH level may be helpful. In the setting of an atypical clinical scenario and normal premenopausal FSH and estradiol levels, other causes of hot flashes should be considered (eg, thyroid dysfunction, infection, carcinoid syndrome, pheochromocytoma, autoimmune disorders, mast cell disorders, malignancies).

Postmenopausal Bleeding

In postmenopausal women with uterine bleeding not caused by vaginal or endometrial atrophy or cervical lesions, endometrial cancer must be excluded, unless the patient is using cycling hormonal therapy. Transvaginal ultrasonography or endometrial biopsy should be considered. Biopsy is indicated if endometrial thickness is more than 5 mm on ultrasonography, other endometrial abnormalities (eg, a focal lesion) are present, or bleeding is persistent. After malignancy is excluded, reassurance is usually sufficient.

Hormone Therapy

Estrogen is the most effective treatment of hot flushes and other menopausal symptoms, but it is associated with potential risks (Box 38.6). Postmenopausal hormone therapy is appropriate for women with moderate to severe symptoms of menopause that interfere with quality of life or activities of daily living. The appropriate dose, duration, regimen, and administration route are considered after weighing individual risks and benefits. Hormone therapy effectively prevents postmenopausal osteoporosis and fractures. For women with an intact uterus, unopposed estrogen increases the risk of uterine dysplasia and malignancy, thus a progestogen (oral or intrauterine) must be used. Women must be made aware that cyclic bleeding will occur when using an oral progestogen.

Box 38.6 • Benefits and Risks of Hormone Therapy (HT)

Benefits

- Reduces hot flushes and night sweats
- Reduces vaginal dryness and dyspareunia
- Reduces postmenopausal osteoporotic fractures
- Reduces risk of new onset of diabetes mellitus
- Associated with decreased risk of colon cancer (estrogen plus progestogen therapy, not estrogen therapy alone)

Risks

- Increases risk of venous thromboembolism
- Increases risk of coronary heart disease[a]
- Increases risk of ischemic stroke
- Increases risk of breast cancer
- Increases risk of dementia when started at age >65 y[b]

[a] Initiation of HT for women older than 60 years or who are more than 10 years from menopause onset causes higher absolute risk of chronic heart disease, venous thromboembolism, and stroke than for women who initiate HT in early menopause.

[b] HT cannot be recommended at any age to prevent or treat a decline in cognitive function or dementia.

Breast Conditions

Evaluation of the Palpable Breast Mass

Breast lumps are common and usually benign. However, benign characteristics are insufficient to exclude cancer. If clinical suspicion is high, negative findings even on mammography and ultrasonography do not definitively exclude cancer.

History should include breast mass location and duration, behavior related to menstrual cycle, associated pain, skin or nipple changes (eg, discharge, excoriation), trauma, and changes before evaluation. Risk factors should be considered, but a lack of defined risk factors does not exclude the possibility of cancer. Physical examination should include visual inspection for asymmetry, puckering, dimpling, nipple lesions or retraction, erythema, and peau d'orange. Palpation should include tissue from the clavicle to the inframammary area and from the sternum to the midaxillary line. The axillary, cervical, and supraclavicular nodal regions should be included.

Initial imaging evaluation includes diagnostic mammography and ultrasonography for women age 30 years or older and ultrasonography alone for women younger than 30 years. Symptomatic simple cysts can be aspirated. Nonbloody fluid does not require cytologic evaluation. A complex cyst should be aspirated to confirm complete resolution of the cyst.

Tissue evaluation options are fine-needle aspiration (FNA), core needle biopsy (CNB), and excisional biopsy. FNA is inexpensive and can be done in an office setting, but the sensitivity and specificity are highly variable. A negative FNA result does not exclude cancer, particularly when clinical or imaging suspicion is high. CNB provides enough tissue for histologic diagnosis and is often done with imaging guidance; it has higher sensitivity and better specimen quality than FNA. Concordance between CNB and excisional biopsy exceeds 90%. Excisional biopsy is reserved for cases in which FNA and CNB are technically unfeasible or when the findings on FNA or CNB are discordant with the physical examination or imaging findings. CNB or excisional biopsy should be done when FNA shows atypical cells. Excisional biopsy should be done when CNB shows atypical hyperplasia (to exclude malignancy).

Mammographic features of malignancy include soft tissue masses or clustered microcalcifications. The most specific mammographic feature of malignancy is a spiculated mass. Calcifications that are large and diffuse or scattered are usually benign, whereas those described as clustered punctate, fine pleomorphic, or fine linear branching are suggestive of malignancy.

KEY FACTS

- ✓ Fibroids—need treatment only if they cause symptoms
- ✓ Before starting topical corticosteroid therapy, confirm the diagnosis of lichen sclerosus with vulvar biopsy
- ✓ Prescribe postmenopausal hormone therapy at the lowest dose and for the shortest time needed to reach treatment goals and after weighing individual risks and benefits
- ✓ If breast calcifications on mammography are large and diffuse or scattered, they are usually benign; if clustered punctate, fine pleomorphic, or fine linear branching, they are usually malignant

Breast Pain

Breast pain (mastalgia) is classified as cyclic, noncyclic, or extramammary. Cyclic mastalgia occurs in premenopausal women. The pain begins in the luteal phase (2 weeks before menses) and resolves or substantially improves with menstruation. Pain is usually diffuse, bilateral, and concentrated in the upper outer aspect of the breasts, but it may be more severe in 1 breast.

Noncyclic mastalgia is not associated with the menstrual cycle; it can affect premenopausal and postmenopausal women. The cause is often elusive, but it may be due to pregnancy, duct dilatation, cysts, fibroadenomas, injury, prior breast surgery, infection, or exogenous estrogen. Breast pain alone is due to cancer in less than 10% of cases, and less than 1% of women with breast pain and normal results on clinical examination and breast imaging have cancer. The evaluation of focal breast pain should include history and clinical examination, age-appropriate mammography, and ultrasonography. Ultrasonography alone should be used for women younger than 30 years who present with focal pain. For women whose history is consistent with cyclic pain and in whom results of clinical examination are negative, reassurance and pain management, depending on severity, are usually sufficient.

For persistent or moderate to severe pain, initial treatment strategies include a well-fitted support brassiere (including nighttime use); heat or cold packs, or both; gentle massage; dietary changes (eg, reduced intake of caffeine and sodium); relaxation techniques; and exercise. Over-the-counter analgesics may be effective. Elimination or adjustment in exogenous estrogen doses may alleviate breast pain. Other hormonal agents may be effective for patients with severe cyclic breast pain unresponsive to conservative measures. Danazol is the only medication with US Food and Drug Administration approval for mastalgia; adverse androgenic effects limit its utility.

Nipple Discharge

Nipple discharge is common in reproductive-aged women and is usually benign. Nipple discharge can be classified as due to ductal lesions or galactorrhea (discharge of milk or milk-like secretions 6 months or more postpartum in a non–breast-feeding woman). Galactorrhea presents as spontaneous, milky discharge from multiple ducts of both breasts as a result of increased serum prolactin. Evaluation and treatment of galactorrhea due to hyperprolactinemia are discussed in Chapter 17, "Pituitary Disorders." Treatment is offered only if the patient is bothered by the discharge, is unable to conceive, or has evidence of hypogonadism or low bone density.

Nipple discharge not due to galactorrhea may be benign or caused by ductal lesions, including malignancy. Benign nipple discharge typically is bilateral, nonbloody, and multiductal, but it may be unilateral. Green, gray, or blue discharge is typical of fibrocystic breast change. Brown or yellow discharge is also usually benign. Clear (watery) discharge is usually benign, but malignancy must be excluded. Pathologic discharge (which may be due to malignancy) is typically unilateral, uniductal, and spontaneous. It is typically bloody, serosanguineous, or, sometimes, watery or clear. The most common cause of bloody nipple discharge is a benign intraductal papilloma, followed in frequency by ductal ectasia (ductal dilatation with or without inflammation) and carcinoma. Various factors can be associated with an increased likelihood of cancer (Box 38.7).

Mammography and ultrasonography should be done for all nonlactating women with nipple discharge who are older than 30 years and ultrasound alone for women younger than 30 years, unless the discharge is unmistakably caused by fibrocystic change. Galactography and ductoscopy are not routinely used in the evaluation of nipple discharge.

Patients with nipple discharge that is neither pathologic nor galactorrhea and with normal diagnostic breast imaging results can be reassured and observed. Patients with pathologic discharge that can be clinically localized to 1 duct should be considered for surgical duct excision, even when imaging results are negative. Figure 38.1 shows a suggested algorithm for the evaluation of spontaneous nipple discharge.

Box 38.7 • Factors That Increase the Likelihood of Cancer Associated With Nipple Discharge

Associated palpable mass

Age >40 y

Grossly bloody, guaiac-positive, serosanguineous, or watery or clear discharge

Unilateral

Spontaneous

Persistent

Single duct

Benign Breast Disease

Simple cysts are the most common cause of discrete benign breast lumps and occur most often between ages 35 and 50 years. Fibroadenomas are the most common solid benign masses; the median age at diagnosis of fibroadenomas is 30 years, but they may occur in postmenopausal women. Benign breast disease has many other histologic classifications. The main importance lies in whether the cysts confer an increased risk of breast cancer. Patients at substantially increased risk should be counseled about appropriate screening and risk reduction options. The magnitude of risk differs depending on the histologic classification (Box 38.8).

Depression and Anxiety

The lifetime prevalence of depression is higher in women than men, and the peak age at onset is lower (from 33 to 45 years in women vs >55 years in men). Women are less likely to commit suicide but twice as likely to attempt suicide, and white women are twice as likely as African American women to commit suicide. Bipolar disorder has no sex difference.

The risk of depressive symptoms and clinical depression increases during perimenopause, whether spontaneous or surgically induced. Postmenopausal estrogen may improve mild depressive symptoms, but it is not sufficient for treatment of clinical depression.

Postpartum depression affects 10% to 15% of women and develops in the first month after childbirth. It is often unrecognized. Risk factors include prior major or postpartum depression, depression during pregnancy, unmarried status, or unplanned pregnancy. It is essential to evaluate thyroid function in postpartum women with depressive symptoms because of overlap in presentation. Psychosis can occur in women with postpartum depression and usually requires acute hospitalization.

Anxiety disorders that are more prevalent in women include panic disorder, agoraphobia, social phobia, generalized anxiety disorder, and posttraumatic stress disorder. An anxiety disorder may underlie persistent somatic concerns. If nonpharmacologic measures are inadequate, combined medication and cognitive behavioral therapy should be offered.

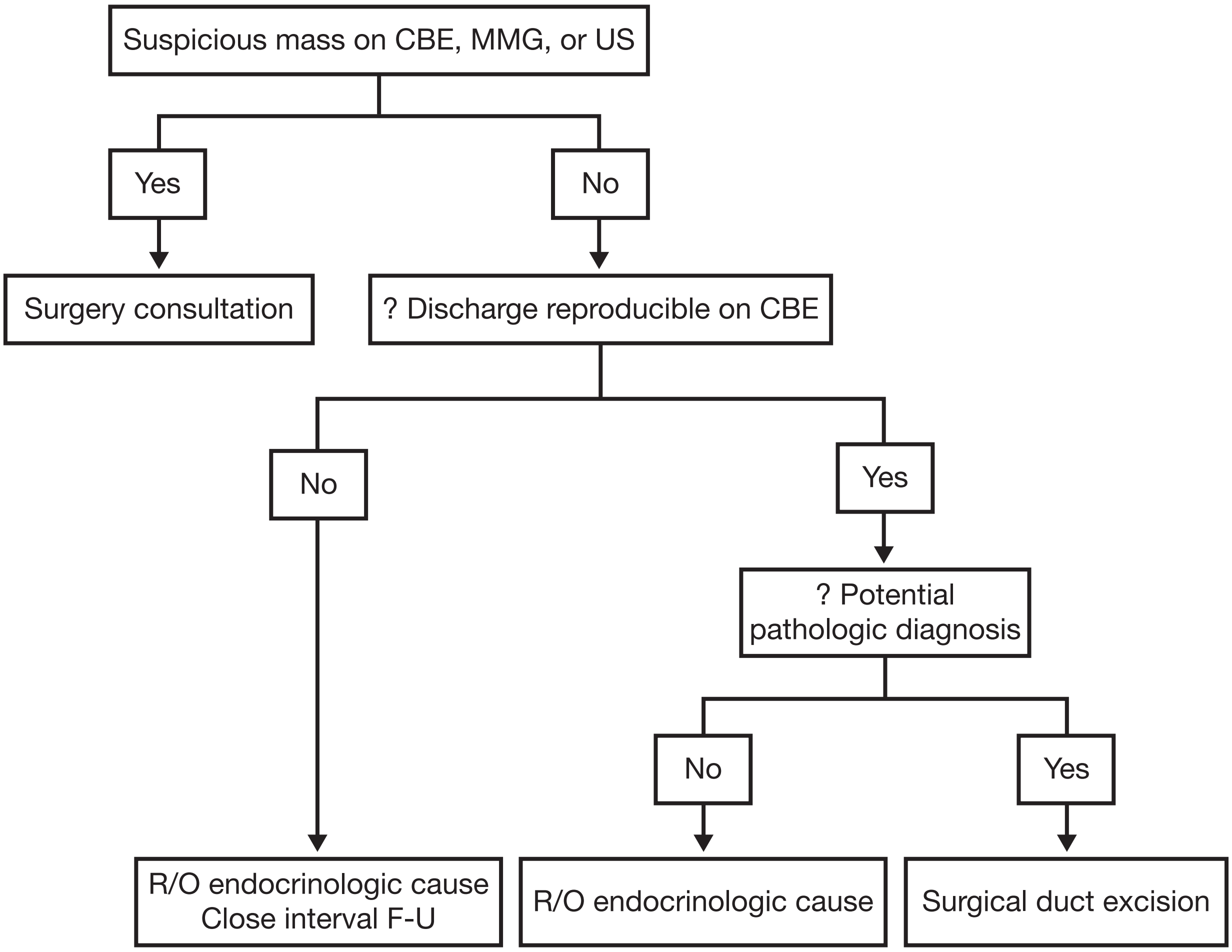

Figure 38.1. *Algorithm for Evaluation of Spontaneous Nipple Discharge. CBE indicates clinical breast examination; F-U, follow-up; MMG, mammography; R/O, rule out; US, ultrasonography.*

The risks and benefits of pharmacologic therapy need to be considered for pregnant or nursing women. Tricyclic antidepressants and some selective serotonin reuptake inhibitors are relatively safe, although there have been isolated adverse reports of infants exposed to these agents through breast milk.

Intimate Partner Violence

Intimate partner violence is intentional controlling or violent behavior. Controlling behavior may include physical or emotional abuse, sexual assault, economic control, or social isolation of the victim. In 95% of reported cases, a man is the perpetrator and a woman is the victim. At least 1 in 3 US women is assaulted by a partner during her lifetime. Female victims most often present for care indirectly related to abuse injuries. Battered women use health services 6 to 8 times more than nonbattered women and have an increased incidence of headaches, sexually transmitted diseases, irritable bowel syndrome, depression, and anxiety. Suggestive aspects of the history include depression, chronic pain syndromes, gastrointestinal tract concerns, an overprotective partner, injuries during pregnancy, frequent visits for injuries, and a history of childhood abuse. All women should be asked about intimate partner violence. Routine prenatal screening for intimate partner violence is particularly important because abuse occurs in 1 of 6 pregnancies and often begins or escalates in early pregnancy.

Suggestive physical examination findings include injuries incompatible with the history, multiple injuries in various healing stages, injuries suggestive of a defensive posture (eg, ulnar fractures), and pattern injuries (eg, burns, choking or bite marks, wrist or ankle abrasions).

Documentation in the health record is essential and may provide evidence to help the victim separate from the perpetrator. If the victim consents, injury photographs should be obtained. Physical evidence should be preserved.

Victims of intimate partner violence need treatment of injuries, support, safety assessment, and referral to appropriate resources to prevent further abuse. A safety assessment by a victim's advocate, social worker, or law enforcement personnel is critical. When these persons are not available, a trained physician

Box 38.8 • Histologic Categories of Benign Breast Disease

- Nonproliferative breast lesions (RR, 1.27)
  - Duct ectasia
  - Fibroadenoma without proliferative epithelial changes
  - Fibrosis
  - Mastitis
  - Mild hyperplasia without atypia
  - Cysts
  - Simple apocrine metaplasia
  - Squamous metaplasia
- Proliferative breast lesions without atypia (RR, 1.88)
  - Fibroadenoma with proliferative epithelial changes
  - Moderate or florid hyperplasia without atypia
  - Sclerosing adenosis
  - Papilloma
  - Radial scar
- Atypia (RR, 4.24)
  - Atypical ductal hyperplasia
  - Atypical lobular hyperplasia

Abbreviation: RR, relative risk.

or nurse should perform a safety assessment. Immediate psychiatric referral should be arranged for patients expressing suicidal or homicidal intentions. The safety assessment must include inquiries regarding children in the home, and any child abuse must be reported to child abuse authorities. Some jurisdictions require reporting to the child abuse authorities any intimate partner violence in a home where children reside. Because intimate partner violence homicides are more likely to occur immediately after separation, ensuring the safety of the victim during separation is critical.

Sexual Assault

Sexual assault is any sexual act performed without consent. Most cases are unreported, and about one-half of victims have some acquaintance with their attacker. A sexual assault victim should be evaluated by a trained sexual assault nurse examiner. Evidence can be collected up to 120 hours after the assault. In certain cases, treatment to prevent sexually transmitted infections and pregnancy may be offered.

Key Definition

Sexual assault: *any sexual act performed without consent.*

KEY FACTS

- ✓ Initial therapies for mastalgia—a well-fitted support brassiere; heat or cold packs, or both; gentle massage; dietary changes; relaxation techniques; and exercise
- ✓ Benign nipple discharge—typically bilateral, nonbloody, and multiductal
- ✓ Pathologic nipple discharge—typically unilateral, uniductal, spontaneous, and bloody, serosanguineous, or, sometimes, watery or clear
- ✓ Document intimate partner violence in the health record; this documentation may provide evidence to help the victim separate from the perpetrator

V

Questions and Answers

Questions

Multiple Choice (Choose the best answer)

V.1. A clinic has access to computed tomography (CT) colonography technology. Its physician knows the prevalence of colon lesions (adenomatous polyps ≥7 mm or cancers) is 10% in the elderly high-risk population that is screened. The physician recently read an article stating that the sensitivity of CT colonography to identify lesions greater than or equal to 7 mm is 60%, with 90% specificity. If the physician uses this CT colonography technique to screen the high-risk elderly population for lesions greater than or equal to 7 mm, what percentage of that group with a positive test actually has an adenomatous polyp or cancer?

a. 40%
b. 60%
c. 80%
d. 90%

V.2. A physician recently read the report of a randomized controlled trial that assessed the efficacy of patient self-management of anticoagulation to reduce bleeding risks. In that study, 1 group of patients was trained to adjust their own warfarin on the basis of international normalized ratio (INR) results obtained using a home INR device. This group was compared with a clinic-based management group of patients who visited their clinic every 4 weeks for INR checks. A physician then adjusted their dose and arranged for the next INR check. At 1 year, the self-management group had a 2% risk of any (major or minor) bleeding events. The clinic-based group had a 7% risk of any bleeding events. On the basis of this information, what number of patients needs to be enrolled in a system of self-management of their anticoagulants for 1 year to reduce 1 adverse event of bleeding?

a. 2
b. 7
c. 14
d. 20

V.3. TableV.Q3 presents likelihood ratios for serum ferritin as a test for iron deficiency anemia among elderly patients. If the prior probability of iron deficiency among elderly patients with anemia is 40%, then what is the posttest probability of iron deficiency when the ferritin value is 55 mcg/L?

Table V.Q3.

Serum Ferritin Level, mcg/L	Interval Likelihood Ratio
>100	0.1
46-100	0.5
19-45	4.0
<19	30.0

a. 15%
b. 20%
c. 25%
d. 30%

V.4. A 52-year-old woman, status post heart transplant, with mild depression presents with symptoms that ultimately lead to the diagnosis of heart transplant rejection. She has taken cyclosporine therapy faithfully during the past year. The only other change has been the use of a dietary supplement, which she started a few months ago to help with her symptoms of depression. Failure of her antirejection regimen was most likely caused by which of the following dietary supplements?

a. S-adenosyl-methionine (SAMe)
b. 5-hydroxytryptophan
c. St John's wort (*Hypericum perforatum*)
d. Folic acid

V.5. A 76-year-old man reports bilateral knee pain. Previously, he received a diagnosis of advanced osteoarthritis of both knees. Prior trials of nonsteroidal anti-inflammatory drugs (NSAIDs) had to be discontinued because of adverse effects (eg, hypertension, renal failure). An adequate trial of acetaminophen did not provide any substantial reduction in his pain. The patient states that a friend of his has found benefit from a supplement, and he would like to know if there is one he could try. Which of the following supplements has been shown to have efficacy in treating the pain of osteoarthritis?

a. Vitamin E
b. Horse chestnut extract
c. S-adenosyl-methionine (SAMe)
d. Shiitake mushroom

V.6. A 65-year-old woman has various medical conditions, including fibromyalgia, low back pain, osteoarthritis, and headache. Cellulitis has also developed involving the medial aspect of the left lower extremity. She would like to incorporate acupuncture as an adjunct treatment of any of her symptoms where there is evidence of potential benefit. Of all of her conditions, which has the least evidence to suggest efficacy of acupuncture as a treatment modality?

a. Chronic headache
b. Cellulitis
c. Fibromyalgia
d. Low back pain

V.7. A 62-year-old woman presents with velvety hyperpigmentation around her neck (Figure V.Q7). She has similar changes in the axillae. What is the most likely associated condition?

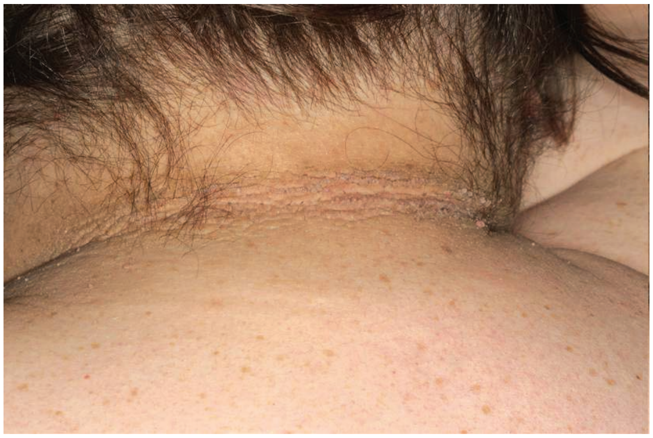

Figure V.Q7.

a. Mitral valve prolapse
b. Occult malignancy
c. HIV infection
d. Type 2 diabetes mellitus

V.8. A 34-year-old woman presented with tender nonulcerative nodules on her lower legs (Figure V.Q8). She denies the use of any new medications. What is the most likely infectious cause?

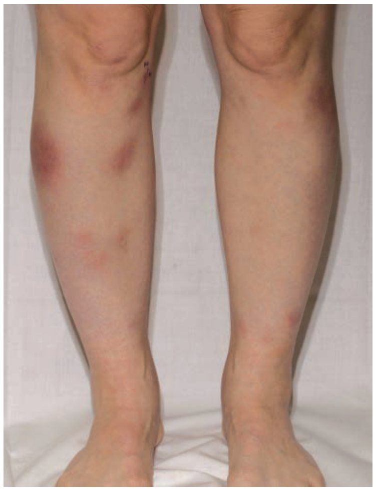

Figure V.Q8.

a. Streptococcal pharyngitis
b. Coccidioidomycosis
c. *Mycoplasma pneumoniae* infection
d. Syphilis

V.9. A patient has a history of ulcerative colitis and has peristomal nonhealing pustular ulcers (Figure V.Q9). What is the best treatment option?

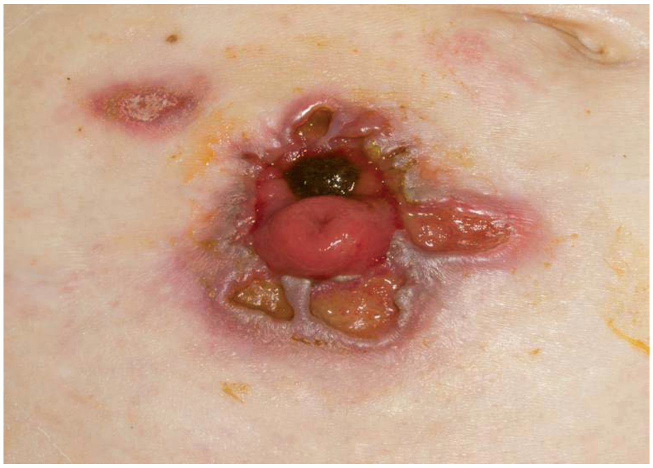

Figure V.Q9.

a. Antibiotics
b. Systemic corticosteroids
c. Surgical débridement
d. Antifungal therapy

V.10. A 19-year-old woman who has chronic multifocal musculoskeletal pain is seen by her primary care physician because she is concerned that she may have Ehlers-Danlos syndrome. She bases this concern on joint hyperextensibility and her mother having similar symptoms. Her mother has not been tested for Ehlers-Danlos. Her father has no history concerning for this syndrome. If the patient's mother is tested and found to have classical Ehlers-Danlos, what is the chance that she would have the abnormal gene as well?

a. 25%
b. 33%
c. 50%
d. 100%

V.11. A 20-year-old man with Down syndrome presents for evaluation of fatigue and dyspnea. These symptoms have gotten worse over the past several weeks. The patient states that he is tired and has trouble breathing but is unable to offer additional history. He is accompanied by a guardian who does not know his health history. He has not had routine primary care throughout his life. He is new to the physician, who has no health records for the patient. What is the next best step in care management?

a. A complete blood cell count (CBC) to screen for acute lymphoblastic leukemia (ALL)
b. Transthoracic echocardiography to look for congenital heart disease
c. Health records obtained
d. A CBC and echocardiography

V.12. A 27-year-old man of Mediterranean descent presented to the emergency department with symptoms of dyspnea, fatigue, nausea, vomiting, and a yellow discoloration of his eyes. He currently receives treatment with trimethoprim-sulfamethoxazole for cellulitis. Testing ordered by the emergency department reported that his hemoglobin was 8.9 g/d; bilirubin was increased at 8 mg/dL. A peripheral blood smear showed hemolytic anemia. The man was admitted to the hospital. Further workup showed a negative Coombs test. What is the most likely cause of his acute hemolytic anemia?

a. Glucose-6-phosphate dehydrogenase (G6PD) deficiency
b. Hereditary spherocytosis
c. Thalassemia
d. Autoimmune hemolytic anemia

V.13. An 82-year-old woman is brought to the clinic by her spouse for unintentional weight loss. She has lost approximately 4 kg (9 lb) in the past 3 months and has decreased interest in food. Her weight is now 42 kg (92 lb) and her body mass index is 17 kg/m^2. Her past medical history is clinically significant for hypertension, well-controlled depression, moderately severe Alzheimer disease, and hypothyroidism. Her medications, all taken orally and daily, include hydrochlorothiazide 25 mg, levothyroxine 25 mcg, mirtazapine 15 mg, donepezil 10 mg, and potassium chloride 20 mEq. Aside from decreased interest in food, the patient is at her baseline condition. She is dependent on her caregiver for bathing and dressing but is able to feed herself without difficulty. She continues to enjoy visits from her family and activities at her assisted living facility. Which of the following is the best first step for managing this patient's weight loss?

a. Increase mirtazapine dose.
b. Hospice care
c. Discontinue donepezil.
d. Feeding tube placement

V.14. An 88-year-old woman with early-stage dementia with Lewy bodies (DLB) is hospitalized following the surgical treatment of a femoral neck fracture. On postoperative day 2, the patient becomes agitated and yells at the nursing staff. After she punches and bites her patient care attendant, risperidone and lorazepam are administered urgently. Which of the following statements is true about this management decision?

a. Atypical antipsychotic medications are the best intervention for hyperactive delirium in the clinical setting of dementia.
b. Atypical antipsychotic medications have been proven to prevent delirium among patients undergoing hip fracture surgery.
c. Benzodiazepines are the only medication approved by the US Food and Drug Administration (FDA) for postoperative delirium.
d. Risperidone increases this patient's risk of extrapyramidal symptoms, stroke, and death.

V.15. A 71-year-old woman presents with intermittent urinary incontinence. She is distressed because she loses urine with coughing and exercise. The patient also reports occasional strong urges to urinate even after she has just voided. She has neither dysuria nor fever. Her past medical history is important for refractory constipation and depression. Medications include senna and paroxetine. Physical examination shows atrophic vaginitis. The patient has no evidence of pelvic organ prolapse. Cough during the examination yields urine leakage. Which of the following is the best next step for this patient?

a. Long-acting tolterodine
b. Behavioral therapy with Kegel exercises
c. Oral menopausal hormone therapy
d. Pessary placement

V.16. A 54-year-old man with a known history of alcohol use disorder presents to the emergency department for alcohol "detoxification." He typically drinks 24 12-oz cans of beer per day, and his last drink was 20 hours ago. During initial evaluation, the patient endorses a moderate headache, anxiety, tremor, and nausea. His laboratory tests show normal blood counts, normal kidney and liver function tests, and a negative blood alcohol level. He is given 2 mg lorazepam and admitted to a medical unit for alcohol withdrawal syndrome (AWS). Shortly after arrival at the unit, the patient has a generalized tonic-clonic seizure that lasted 20 seconds and terminated without pharmacologic intervention. After it, the patient denies physical symptoms, but he appears encephalopathic. He is unaware of his physical location, the date, or the reason he is hospitalized, and he has hallucinations. Which of the following is the next best step in treatment of this patient's AWS?

a. Scheduled lorazepam administration, with a taper as the patient's symptoms resolve
b. Lorazepam administration as needed, with dosing and frequency based on the severity of the symptoms (ie, symptom-trigger therapy)
c. Scheduled levetiracetam and haloperidol administration
d. Scheduled clonidine and haloperidol administration

V.17. A 73-year-old male resident of a skilled nursing facility was evaluated in the emergency department for confusion. His creatinine value was 2.8 mg/dL—indicative of acute renal failure—believed to be due to dehydration. The man was admitted to the hospital. On hospital day 3, his acute renal failure resolved but he had a fever, which was associated with a cough and left basilar crackles. Chest radiograph showed a left lower-lobe infiltrate. His temperature was 37.1°C; respiratory rate, 14 breaths per minute; heart rate, 92 beats per minute; blood pressure, 138/68 mm Hg; and oxygen saturation, 94% on room air. The patient's white blood cell count was 16,200/μL; hemoglobin, 11.4 mg/dL; hematocrit, 34%; sodium, 134 mEq/L; and creatinine, 1.1 mg/dL. The hospital antibiogram indicates that 28% of *Staphylococcus aureus* isolates are oxacillin resistant. The patient has no drug allergies. What is the next best step in treatment of this patient?

a. Start levofloxacin and vancomycin therapy.
b. Start piperacillin-tazobactam and cefepime therapy.
c. Start cefepime and metronidazole therapy.
d. Start therapy with cefepime, levofloxacin, and vancomycin.

V.18. A 92-year-old woman is brought to the emergency department from her nursing home because of fever, confusion, respiratory distress, and presumed infection. Given her confusion, the woman is not able to make her own medical decisions. She is a widow, accompanied by 2 of her children. She does not have an advance directive. What is the best question to ask her children about the care of this patient?

a. "If your mother could express her wishes about her medical care, what would they be?"
b. "What are your wishes for the best care of your mother?"
c. "Would you like to confer with a social worker about your mother's care?"
d. "Would you like to have the court appoint someone to make decisions for your mother about her care?"

V.19. A physician in a clinic has a pattern of arriving late to work. Recently, the physician was on vacation, and in her absence, a separate staff physician saw several of her patients for follow-up.

The staff physician notes that she neglected to complete her clinic notes on several patients who had been seen recently. One of the patients had a critical laboratory test value that was not acted on appropriately. When the physician returns from vacation, the staff physician confronts her about these behaviors. She becomes angry. What is the next best step in management of the situation?

a. Discuss with the physician's nurse whether the nurse has noticed any patient care issues.
b. Check with the state board to learn whether the physician has had a filing of prior complaints.
c. Report these findings to the physician's supervisor.
d. Review the laboratory test findings for her patients to prevent an error.

V.20. A 65-year-old man presents with report of decreased urinary stream and increased frequency of nocturia over the past year. He denies fevers, dysuria, weight loss, or back pain. He expresses feeling really bothered by his symptoms and would be interested in medical treatment. His American Urological Association International Prostate Symptom Score (AUA/IPSS) is 10. On physical examination, he appears obese and comfortable. Digital rectal examination reveals a smooth, symmetrically enlarged prostate of approximately 40 cc in volume. Of note, his prostate-specific antigen (PSA) level 1 year ago was 0.74 ng/mg. A clean-catch urinalysis with microscopy shows normal results. Which of the following is the preferred next step for this patient?

a. Observation
b. Cystoscopy
c. Finasteride therapy 1 mg by mouth daily
d. Tamsulosin therapy 0.4 mg by mouth daily

V.21. A 54-year-old man presents with a report of increased urinary frequency over the past several weeks. Additionally, he has new nocturia 1 to 3 times nightly. His only other symptom is nasal congestion that seems improved with over-the-counter medications. His only past medical history is erectile dysfunction (ED), which he has been treating successfully with sildenafil approximately once weekly for the past 2 years. On physical examination, the patient appears alert and comfortable. Head and neck examination is remarkable for postnasal drainage that is visible in the posterior oropharynx. Digital rectal examination shows a slightly enlarged prostate, approximately 30 cc in volume, with no nodules or tenderness. Which of the following is the preferred next step in the care of this patient?

a. Obtain a prostate-specific antigen blood test
b. Obtain a urinalysis with microscopy
c. Discontinue sildenafil therapy
d. Discontinue over-the-counter medications

V.22. A 68-year-old man presents with a report of erectile dysfunction (ED) for several years. He occasionally has erections sufficient for vaginal penetration although not frequently. He has a good relationship with his wife, but the ED has limited their intimacy. This change in intimacy causes him some distress, yet he denies sadness or depressed mood. The patient no longer has nocturnal erections. His past medical history includes obesity, hypertension, hyperlipidemia, and coronary artery disease without previous coronary interventions. His medications are metoprolol, aspirin, and atorvastatin. He does not take nitrate medications. He reports being deconditioned to the point where he cannot walk up several flights of stairs. On physical examination, he is obese (body mass index, 38). Auscultation of his heart and lungs is normal. His penis is circumcised, normal appearing, and without any angulation or palpable nodularity in the stretched position. Testes are descended bilaterally, normal volume, and without varicosities. What is the preferred next step in the care of this patient?

a. Obtain a cardiac stress test.
b. Obtain a total testosterone level.
c. Prescribe sildenafil 50 mg by mouth as needed.
d. Prescribe tadalafil 10 mg by mouth as needed.

V.23. A 49-year-old man presents with a report of erectile dysfunction (ED) for several months. He has had numerous sexual partners over the past year and says that his performance is sometimes poor with respect to an ability to achieve and maintain erections. His sexual interest is strong and his energy level is normal. He acknowledges having nocturnal erections. The patient denies feeling depressed. His only past medical history is hypertension, which has been effectively treated with hydrochlorothiazide for the past 5 years. On physical examination, his affect is bright and he appears physically fit. Examination of his genitalia is normal. Laboratory testing is normal, including complete blood cell count and thyrotropin (TSH). Fasting morning serum testosterone level is 325 ng/dL. What is the preferred next step for this patient?

a. Repeat a fasting morning total testosterone level.
b. Initiate topical testosterone 1% gel at 50 mg daily.
c. Initiate citalopram 20 mg by mouth daily.
d. Prescribe vardinafil 10 mg by mouth as needed.

V.24. A 32-year-old woman presents to the acute care clinic for evaluation of a sore throat that began 48 hours prior. She reports caring for her 3-year-old daughter who was treated with antibiotics for strep throat 1 week ago. The patient is coughing throughout the visit. Her temperature is 37.0°C. On examination, she has tender anterior cervical lymphadenopathy but no tonsillar exudates. Her heart has a regular rate and rhythm; lungs are clear to auscultation bilaterally. Which of the following is the next best step?

a. Rapid streptococcal antigen testing
b. Throat culture
c. Empirical treatment with amoxicillin
d. Observation and symptomatic treatment

V.25. A 65-year-old Asian woman presents to the clinic for evaluation of acute onset of a painful, red left eye. No trauma occurred before the onset of her symptoms. She notes the presence of halos around lights and blurriness to her vision. The patient reports a headache and nausea. On examination, diffuse conjunctival erythema is seen, and a 5-mm pupil is unreactive to light. The cornea is cloudy. What is the next best step in the care of this patient?

a. A dilated funduscopic examination
b. Emergent referral to an ophthalmologist
c. Prednisolone acetate 1% ophthalmic drops
d. Ofloxacin 0.3% ophthalmic drops

V.26. A 27-year-old man presents to the urgent care clinic for concerns of conjunctivitis. He notes that 24 hours ago, his left eye became red and felt gritty and irritated. He has had watery discharge from the eye and notes that this morning the right eye began to be involved as well. He has a 2-year-old son in daycare with similar symptoms who was required to have antibiotic eye drops in order to return to daycare. The man asks for the same care. On examination, the patient is afebrile. He has bilateral conjunctival injection with clear, watery discharge. What is the most appropriate next step?

a. Erythromycin 5 mg/g ophthalmic ointment
b. Over-the-counter lubricating eye drops
c. Prednisolone acetate 1% ophthalmic drops
d. Obtain a swab of the discharge and send it for culture.

V.27. A 64-year-old man was admitted to the hospital with end-stage liver failure in the clinical setting of underlying cryptogenic cirrhosis. He is now in the intensive care unit (ICU) with multisystem organ failure. He is unresponsive and receives both mechanical ventilation and vasopressors. The medical teams caring for him agree that he has little chance of surviving this hospitalization. A hospitalist is caring for this patient, and the ICU team has asked the hospitalist to participate in a family meeting to determine the next steps of care. The hospitalist notes that the patient does not have an advance directive on file. According to state law, in the absence of an advance directive naming a proxy decision maker, the man's wife is the legal decision maker. The hospitalist participates with the ICU team in a family care conference with the patient's wife and their 3 adult sons. In that meeting, the family is told that the patient is dying and is unlikely to survive the hospitalization. His sons state that they do not think the patient would want to die in the ICU while receiving care from machines, and they describe numerous conversations with the patient supporting that preference. The patient's wife agrees with the sons in theory, but she also states, "I can't give up on him. I can't be responsible for that. I'll always wonder if I did the right thing." Which of the following is the best next step in management?

a. An ethics consultation
b. Family focus on what the patient himself would prefer under the circumstances
c. Transition the patient's care to comfort care, on the basis of his previously expressed preferences and the medical situation.
d. Acknowledgment of the difficulty of the situation and recommendation to meet again tomorrow

V.28. The patient is a 59-year-old woman with a 45-year history of type 1 diabetes mellitus, complicated by end-stage renal disease. She has received thrice-weekly hemodialysis for 12 years. She is admitted to the inpatient medicine service for management of several severely painful wounds on her lower extremities and abdomen, consistent with calciphylaxis. A clinician is called to the patient's bedside for uncontrolled pain that she rates at 10 of a 0-to-10 pain scale. She received a 10-mg dose of oral oxycodone 1 hour ago, without pain improvement. Which of the following is the best next step in the management of this patient's acute pain?

a. Oxycodone 15 mg orally once now
b. Hydromorphone 8 mg orally once now
c. Morphine 5 mg intravenously once now
d. Hydromorphone 0.8 mg intravenously once now

V.29. The patient is a 75-year-old man with widely metastatic adenocarcinoma of the prostate, including diffuse spinal metastases. He currently receives androgen deprivation therapy, and his disease is stable. His comorbidities are well managed and include hypertension, stage B heart failure following a myocardial infarction at age 65 years, stage 2 chronic kidney disease, and depression. He presents to the outpatient clinic with increasing back pain that he describes as a deep, aching sensation in his low back, associated with painful burning in his buttocks and thighs bilaterally. The pain is moderately severe and affects his ability to walk and perform most of his activities of daily living. Imaging shows his known bony metastases with no evidence of malignant spinal cord compression. Nonmalignant spinal stenosis is present, however, at levels L3 through L5. In the past, he has received epidural corticosteroid injections to his lumbar spine without relief. He also tried gabapentin, which he tolerated poorly because of confusion. He tolerates regularly scheduled acetaminophen (3 g/day), but he does not find it effective. Which of the following is the best next step in managing this patient's pain?

a. Tramadol 50 mg orally every 6 hours as needed for pain
b. Hydromorphone 2 mg orally every 4 hours as needed for pain
c. Ibuprofen 600 mg orally every 6 hours as needed for pain
d. Fentanyl transdermal patch 25 mcg/hour, changed every 72 hours

V.30. A 55-year-old general internist has been feeling more burned out at the end of her work week. Which of the following is not a standard domain of burnout?

a. Emotional exhaustion
b. Fatigue
c. Depersonalization
d. Decreased sense of personal accomplishment

V.31. A 44-year-old general internist reports concern about feelings that he now realizes align with the definition of burnout. In the advice provided to him about physician burnout, which of the following statements is most accurate?

a. Burnout is uncommon, with symptoms affecting less than 10% of physicians.
b. Solutions to burnout are best seen as the responsibility of each individual physician.
c. Physicians with burnout are more likely to reduce their full-time employment (FTE).
d. Burnout rates among internal medicine physicians are lower than other physician averages.

V.32. A 34-year-old physician wishes to reduce her risk of burnout as she begins her long-desired career as a hematologist. Which of the following approaches has been shown to reduce burnout?

a. Participation in small groups to promote community and meaning
b. Increased weekly work hours to maximize income
c. Change in specialty to one with a lower burnout rate
d. Reduced sleep time to ensure that patient charts are kept current

V.33. A 68-year-old woman presents for preoperative evaluation before left hip replacement. She has a history of type 2 diabetes mellitus requiring insulin therapy; hypertension; stage III chronic kidney disease; hyperlipidemia; and coronary artery disease status post 2 drug-eluting stent placements 3 years prior for non–ST-segment elevation myocardial infarction. The patient reports that over the past 3 years, she has participated in a water aerobics program several times per week and is able to climb a flight of stairs. She has been feeling well and has no cardiopulmonary symptoms at this time. Laboratory evaluation is unremarkable except for a stable creatinine of 2.1 mg/dL. Electrocardiography shows normal sinus rhythm, a heart rate of 62 beats per minute, and nonspecific ST-T wave changes in the anterolateral leads. What is the next best step in cardiac assessment before this surgery?

a. Echocardiography
b. Exercise stress test

c. Stress echocardiography
d. No further cardiac testing

V.34. A 70-year-old man presents for preoperative evaluation before elective left knee replacement. Six months ago, he had placement of a drug-eluting stent to the right coronary artery for stable angina. He has had excellent results with no ongoing cardiopulmonary symptoms. He continues to take dual antiplatelet therapy with clopidogrel and aspirin. What is the most appropriate recommendation for perioperative antiplatelet therapy for this patient?

a. Delay elective surgical procedure until 12 months of dual antiplatelet therapy has been completed.
b. Hold clopidogrel for 5 to 7 days before surgery and continue aspirin therapy at 81 mg daily without interruption.
c. Continue both clopidogrel and aspirin therapy throughout the perioperative period.
d. Hold both antiplatelet agents for 5 to 7 days before the procedure.

V.35. A 70-year-old man is scheduled for a right femoral-popliteal bypass graft for severe claudication. Surgery is scheduled in 2 weeks. He is new to the clinic and has a history of coronary artery disease, active tobacco use, moderate chronic obstructive pulmonary disease, hypertension, and left ventricular systolic heart failure with an ejection fraction of 45%. He is asymptomatic during the visit, with the exception of leg pain with activity, and is able to climb a single flight of stairs without cardiopulmonary symptoms. His current medications include aspirin, metoprolol, losartan, and tiotropium. Vital signs are blood pressure, 120/69 mm Hg; pulse, 65 beats per minute; and respirations, 15 per minute. What medication change should be made before surgery?

a. Add clonidine.
b. Start simvastatin therapy.
c. Discontinue metoprolol therapy.
d. Discontinue aspirin therapy.

V.36. A 38-year-old healthy man presents for a general medical evaluation. He is a nonsmoker and takes no medications. He has a family history of colon cancer of his father at age 55 years. On physical examination, the man's blood pressure is 120/80 mm Hg; heart rate, 65 beats per minute; respiratory rate, 16 breaths per minute; and body mass index, 24. He otherwise has no acute reports or concerns. When should he begin colon cancer screening?

a. Initiate colon cancer screening now.
b. At age 40 years
c. At age 45 years
d. At age 50 years

V.37. A 67-year-old woman presents to the clinic to establish primary care. She has had limited prior clinical care. She currently is asymptomatic but is interested in updating her preventive services. She is inquiring about cervical cancer screening. Her only Papanicolaou (Pap) smear was performed 3 years ago and was normal. Human papillomavirus (HPV) cotesting was not performed. What is the best screening recommendation for this patient?

a. Because cervical cancer screening is recommended for women up to age 65 years, this patient needs no further screening.
b. Cervical cancer screening should be repeated in 2 years.
c. Cervical cancer screening should be repeated now.
d. Cervical cancer screening should be performed, in addition to screening for chlamydia, gonorrhea, syphilis, hepatitis B, and HIV infection.

V.38. A 48-year-old man comes to the clinic to establish care. His household consists of him and his wife. He has his previous immunization records available and is up to date on his childhood immunizations and his influenza and tetanus immunizations (he previously received the tetanus-diphtheria-acellular pertussis vaccine). This man's past medical history includes diabetes mellitus well controlled with metformin and glipizide, hypertension well controlled with lisinopril, and hyperlipidemia well controlled with atorvastatin. He has not had any surgical interventions. He is ready to take any immunizations deemed beneficial. He has no travel plans at this time. What are the best immunizations for this man on the basis of his age and comorbidities?

a. Pneumococcal conjugate vaccine 13 (PCV13) and pneumococcal polysaccharide vaccine 23 (PPSV23)
b. Hepatitis B and PPSV23
c. Hepatitis B and PCV13
d. Hepatitis A, hepatitis B, PCV13, and PPSV23

V.39. An 84-year-old woman is admitted to the intensive care unit with altered mental status and septic shock. Two days later, the discovery is made that she was actually in a myxedema coma and had not been taking her prescribed thyroid hormone replacement medication. After further review, the sentinel event committee finds that the patient's medications had not been appropriately reconciled at hospital admission. Which of the following quality improvement methods would best address the care gaps related to medication reconciliation?

a. Plan, Do, Study, Act (PDSA) cycle or model for health care improvement methodology
b. Case management
c. Benchmarking
d. Computerized physician order entry implementation

V.40. In the internal medicine clinic, a physician has noted long wait times, nonstandardized practices, and general dissatisfaction with the rooming process among providers and patients. Which quality improvement methodology could be used to improve the overall rooming process?

a. Process mapping
b. Lean methodology
c. Affinity diagramming
d. Failure mode effects analysis

V.41. A recent audit at a large academic hospital noted below-average rates of effective hand hygiene. Which of the following strategies would be the most appropriate first step?

a. Start educational sessions and scheduled lectures on the importance of hand hygiene.
b. Install additional hand hygiene stations and sinks in high-traffic areas.
c. Explore the processes and system factors that may be contributing to poor hand hygiene.
d. Begin observations of hand hygiene compliance and publish performance reports comparing appropriate rates by hospital unit.

V.42. A 52-year-old woman reports daily hot flushes that are embarrassing her in meetings and night sweats that are disturbing her sleep. She has missed her last 2 menstrual cycles. She is otherwise healthy with a recent normal mammography and has no family history of breast cancer or early heart disease. Which of the following is true regarding management of this patient?

a. Menopausal hormone therapy (MHT) is contraindicated because she is not postmenopausal.
b. She would benefit from MHT for cardioprotection.
c. She would benefit from MHT to relieve her vasomotor symptoms.
d. She would benefit from MHT to prevent dementia.

V.43. A 19-year-old woman is 20 weeks pregnant. She is a college student living in a dormitory on a university campus. She asks you about immunization for human papillomavirus (HPV) because she is worried about exposure from her partner. She received 1 vaccination before becoming pregnant. What is the next best step in management of this patient?

a. She may receive the remaining series of HPV while she is pregnant.
b. She needs to wait until after her pregnancy to receive the remaining HPV vaccinations of the series.
c. In addition to the HPV vaccine, she should also receive tetanus-diphtheria-acellular pertussis (Tdap) vaccine at this time.
d. She should not receive a *Meningococcus* immunization until after her pregnancy.

V.44. A 42-year-old healthy woman presents for evaluation of recent nipple discharge. Her last mammography was 7 months prior and showed dense tissue with no identified abnormalities. She has no prior history of breast abnormalities and no family history of breast cancer. She reports that she woke up 1 morning with spots of blood on her nightshirt over the left nipple area. Two weeks earlier, she found spots of blood in the left cup of her bra. The woman has had no trauma, cannot feel any lumps, and has noticed no changes in appearance of the left breast. She has not had any breast pain or other symptoms. On clinical examination, no visual abnormalities or palpable lumps are detected. Blood is expressed easily from a single duct in the left nipple during examination. What is the next best step for her management?

a. Breast magnetic resonance imaging (MRI)
b. Referral to a surgeon for biopsy
c. Reassurance and observation
d. Diagnostic left mammography and diagnostic ultrasonography

Answers

V.1. Answer a.

A 2×2 table must be constructed to determine the positive predictive value for the CT colonography test among high-risk patients evaluated for colon polyps 7 mm or greater (Table V.A1).

$$\text{The correct answer is } a/a+b \text{ or } 60/150 = 40\%.$$

Table V.A1.

		Disease Present	Disease Absent	
Diagnostic Test Result	**Positive**	60 a	90 b	150 a+b
	Negative	c 40	d 810	c+d 850
		a+c 100	b+d 900	a+b+c+d 1,000

V.2. Answer d.

The physician is asked to determine the number needed to treat (NNT) in a randomized controlled trial that showed that the self-management anticoagulant therapy group had a bleeding event rate of 2%, or an experimental event rate (EER) of 2%. The usual-care group had an EER of 7%, or a control event rate (CER) of 7%. The formula for NNT is $\frac{1}{\text{ARR}}$, where ARR means absolute risk reduction. The calculation is ARR = (CER – EER) or, in this case, 7%–2% = 5%. Therefore, NNT = 1/.05 = 20.

V.3. Answer c.

The first step is to convert the pretest probability of 40% to pretest odds: $\text{Odds} = \text{Probability} / (1 - \text{Probability}) = 0.4 / 0.6 = 0.667$. Then multiply pretest odds by the likelihood ratio to get posttest odds: 0.667×0.5 = 0.33. Finally, convert these posttest odds back to probability: $\text{Probability} = \text{Odds} / \left[1 + \text{Odds}\right] = 0.33 / 1.33 = 0.25 \left(\text{or } 25\%\right)$.

V.4. Answer c.

St John's wort is a popular dietary supplement that induces the CYP3A4 subenzyme system and intestinal P-glycoprotein. As a result, considerable drug level reductions of medications metabolized by this pathway are common, including antirejection drugs such as cyclosporine. The SAMe, 5-hydroxytryptophan, and folic acid do not interact with cyclosporine immunosuppression.

V.5. Answer c.

Clinical trial evidence has shown that SAMe can reduce symptoms related to osteoarthritis. Because it does not share a mechanism of action with NSAIDs, SAMe can be considered for patients with arthritis symptoms who are intolerant of NSAIDs. There is no clinical evidence to support vitamin E, horse chestnut extract, or shiitake mushrooms in the treatment of arthritis symptoms.

V.6. Answer b.

There is no evidence to suggest that infections, including cellulitis, can be treated effectively with acupuncture. Current clinical trial data are generally supportive for a role of acupuncture in the treatment of chronic headache, fibromyalgia, and low back pain.

V.7. Answer d.

This patient has acanthosis nigricans, which are velvety brownish plaques that most commonly occur in intertriginous areas (neck, axillae, and inguinal folds). The most commonly associated conditions are entities with insulin resistance, including diabetes mellitus, obesity, and polycystic ovarian syndrome. Rarely, acanthosis nigricans can be paraneoplastic and develop as a sign of internal malignancy. This should be considered in atypical settings such as a nonobese patient with rapid progression of acanthosis nigricans or involvement in atypical locations. In the early stage of HIV infection, cutaneous manifestations include genital warts, genital herpes, psoriasis, seborrheic dermatitis, xerosis, and pruritic papular eruption and not acanthosis nigricans. Mitral valve prolapse can be seen in patients with pseudoxanthoma elasticum, with pebbly yellowish texture along the neck line.

V.8. Answer a.

Symmetrical, tender, and erythematous subcutaneous nodules on the anterior lower legs are a typical presentation for erythema nodosum. More proximal involvement or ulceration should raise concern for other forms of panniculitis. Erythema nodosum can have numerous causes (infection, medications, sarcoidosis, and inflammatory bowel disease), but in many cases, it is idiopathic. All of the listed infectious causes could be a potential trigger, but streptococcal pharyngitis is most common. Coccidioidomycosis is a common cause in endemic areas. With this patient's demographic characteristics, oral contraceptive pills may be a likely cause. Treatment includes identification of any potential underlying cause and symptomatic relief.

V.9. Answer b.

This patient has pyoderma gangrenosum, which is a neutrophilic disorder leading to ulcerations of the skin. This associated diagnosis of ulcerative colitis and development in a site of trauma is a typical clinical scenario. Other potential associated underlying systemic conditions in pyoderma gangrenosum include Crohn disease, hematologic disorders, and inflammatory arthritis. The lower extremities are a common site of involvement, but attention should be given to potential exacerbation in a site of trauma (including iatrogenic trauma such as a surgical procedure). Skin biopsy may be supportive of the diagnosis, but primarily, the diagnosis is made through the clinical setting, exclusion of other causes for ulceration, and rapid response to systemic corticosteroids. Antibiotics, surgical débridement, and antifungal therapy are not effective in the management of pyoderma gangrenosum.

V.10. Answer c.

Ehlers-Danlos is an autosomal dominant condition. Inheritance of Ehlers-Danlos varies by type. Any child born to a person with classical Ehlers-Danlos has a 50% chance of inheriting the abnormal gene.

V.11. Answer b.

It is unknown whether the patient has had congenital heart disease ruled out at a medical center elsewhere. A congenital heart disease assessment should be performed, especially given his presenting symptoms and history of Down syndrome. A CBC is reasonable in evaluation of dyspnea and fatigue. However, ALL occurs most commonly in children with Down syndrome. Evaluation for ALL should be done at this time, given the history, with no wait for health records to arrive.

V.12. Answer a.

G6PD is the most frequent human enzyme defect. It is common in African, South American, Asian, and Mediterranean populations. Patients may have hemolytic anemia due to infection, fava ingestion, or medications, including antimalarials (primaquine and chloroquine), sulfa drugs, and isoniazid. Coombs test is negative because G6PD is not immune mediated. Hereditary spherocytosis is also Coombs negative, but the clinical picture is not suggestive of this diagnosis; the clinical picture is not suggestive of thalassemia or autoimmune hemolytic anemia.

V.13. Answer c.

Several factors could lead to this patient's weight loss. However, it is important to recognize that adverse drug effects are a common cause of anorexia and weight loss among older adults. Weight loss, diarrhea, and nausea are among the most common adverse effects associated with cholinesterase inhibitors such as donepezil. Although mirtazapine can increase appetite and promote weight gain, these effects are more prominent with lower doses of the medication. In addition, this patient does not show signs of depression at this time. Given her preserved functional capacities, she is not a candidate for hospice services. Feeding tubes have not been shown to prolong life or improve important health outcomes among patients with dementia.

V.14. Answer d.

This patient has acute hyperactive postoperative delirium. Currently, there are no FDA-approved pharmacologic treatments for the management or prevention of delirium. Nonpharmacologic interventions are preferred over pharmacologic therapies. Atypical antipsychotic medications are associated with numerous adverse outcomes among older adults with delirium, including increased risk of stroke, falls, and death. Risperidone is an especially worrisome medication for this patient, given her history of DLB and increased vulnerability to extrapyramidal adverse effects. Benzodiazepines can cause or worsen postoperative delirium and therefore are not an effective treatment strategy.

V.15. Answer b.

This patient likely has both stress incontinence and urge incontinence, with the former being more bothersome to her. The best first-line management strategy for stress incontinence is behavioral therapy, including pelvic floor muscle training (Kegel exercises). Tolterodine is an effective treatment of urge incontinence. However, this antimuscarinic medication will likely make the patient's constipation worse and may prove to worsen other anticholinergic symptoms associated with paroxetine. Oral estrogen has been shown to worsen incontinence. A pessary is appropriate given she does not have pelvic organ prolapse.

V.16. Answer a.

This patient, presenting with AWS, had an AWS-related seizure shortly into his hospital stay. Scheduled benzodiazepines (eg, lorazepam) should be used to prevent further complications of his AWS and tapered as his symptoms improve. Symptom-triggered therapy is appropriate only for patients with normal mentation who are able to verbalize their symptoms. Clonidine and haloperidol are adjunctive therapies for AWS but should not replace benzodiazepines for patients with moderate-to-severe symptoms. Levetiracetam is unnecessary for AWS-related seizures.

V.17. Answer a.

The patient's diagnosis is hospital-acquired pneumonia because the symptoms were not present on admission and developed after 48 hours of hospitalization. He is receiving treatment in a facility where more than 20% of *S aureus* isolates are methicillin-resistant. Therefore, his treatment should include vancomycin. The patient has not received intravenous antibiotics in the past 30 days, and hence he does not have risk factors for multidrug-resistant pathogens and does not require double coverage for *Pseudomonas aeruginosa*. Therefore, levofloxacin with vancomycin is an appropriate antibiotic regimen for this patient.

V.18. Answer a.

When a patient lacks decision-making capacity, the surrogate has an ethical and legal obligation to make decisions on the basis of the patient's preferences. Therefore, asking the children what their mother's wishes would be for her medical care is the best choice in this case. A surrogate should not make decisions on the basis of surrogate's own values and preferences. Providers should not defer the discussion of these issues to persons who are not related to the patient, such as a social worker. Finally, a court-appointed decision maker is not necessary in this case because the patient's children are present and would delay care.

V.19. Answer c.

Physicians have a moral, professional, and legal obligation to report impaired or incompetent colleagues to the appropriate authorities. Therefore, a report of the observed behaviors to the physician's supervisor is necessary and required. A discussion of the situation with the physician's nurse or a check with the state board to see whether prior complaints have been filed does not change the current need to report the concern. Review of laboratory test results for her patients to prevent an error is not sustainable and does not address the core problem.

V.20. Answer d.

Tamsulosin is first-line therapy for benign prostatic hyperplasia (BPH). The American Urological Association recommends a treatment strategy for men with sufficiently bothersome symptoms from BPH (AUA/IPSS >8). BPH may be managed with a broad range of strategies, from observation to medications and even invasive therapy. Observation is a reasonable option for this patient. However, the choice should be based on shared decision making, and this patient has expressed a desire for medical therapy. Cystoscopy would be indicated for only the presence of red flag symptoms such as persistent gross hematuria, which this patient does not have. Finasteride is not the first-line treatment of BPH. Of note, this patient had a PSA value of 0.74 within the past year. Research has shown that men older than 60 years with PSA values in the fractional range have a negligible chance of ever having symptomatic prostate cancer.

V.21. Answer d.

Over-the-counter medications for treatment of nasal congestion, which this patient has, often contain anticholinergic components known to cause urinary retention and lower urinary tract symptoms (LUTS), especially for middle-age men with some degree of prostate enlargement and who have an underlying risk of LUTS. Therefore, the first step for this patient is to discontinue the over-the-counter medication he takes for nasal congestion. In other situations where the cause of LUTS is not clear, it would be reasonable to check a urinalysis and to ensure that his prostate cancer screening was up to date, according to his wishes. Although sildenafil is known to cause nasal congestion as a common adverse effect, he has taken this medication regularly for 2 years with no difficulties.

V.22. Answer a.

For patients with known heart disease and inability to endorse a history of adequate physical exertion (eg, 4 metabolic equivalents), the recommendation is to first obtain cardiac stress testing to stratify the risk of phosphodiesterase type 5 inhibitor therapy, such as sildenafil or tadalafil, before prescribing these medications. For most patients with ED, testosterone levels are not necessary in the absence of evidence for hypogonadism.

V.23. Answer d.

This patient has ED with no apparent risk factors for taking a phosphodiesterase type 5 inhibitor medication such as vardinafil, which would be reasonable to prescribe. On the basis of his clinical evaluation, there is no clear reason to obtain additional testing to exclude medical causes for ED. Nonetheless, his serum testosterone is within normal limits, and without clinical evidence for hypogonadism, there would be no justification for testosterone replacement therapy. Similarly, there is no reason to treat him for depression.

V.24. Answer d.

This patient has acute pharyngitis. She is afebrile and has a cough. She has no tonsillar exudates but has anterior cervical lymphadenopathy. On the basis of the Centor clinical prediction criteria, her Centor score is 1. Patients with fewer than 3 Centor criteria are unlikely to have group A streptococcal pharyngitis (GAS), and therefore this patient should not receive antibiotic therapy or diagnostic testing. If she had 3 criteria, then rapid streptococcal testing would be the next step. Throat cultures are obtained only when antigen testing is negative with a high suspicion for GAS. Empirical treatment without testing is provided when all 4 criteria are met.

V.25. Answer b.

This patient's clinical presentation is concerning for acute angle-closure glaucoma. She should be emergently referred to an ophthalmologist for evaluation and treatment because glaucoma damage to the optic nerve can occur in a matter of hours in acute angle-closure. Dilation of the patient's eye should be avoided because it can exacerbate the condition. Corticosteroid eye drops would be appropriate for a patient with iritis, which can present with a painful red eye, blurred vision, photophobia, and a constricted pupil. Because of the similarities in presentation, however, urgent evaluation by an ophthalmologist still is advised rather than treatment based on the office examination. Antibiotic eye drops are used to treat bacterial conjunctivitis. Although the conjunctiva is erythematous and the eye irritated, bacterial conjunctivitis would involve a change in pupillary size and reaction to light, no change in visual acuity, and the presence of discharge.

V.26. Answer b.

The patient's presentation is consistent with viral conjunctivitis. He has acute onset of erythema and a gritty feeling to the eye with clear, watery discharge. It is common for 1 eye to be affected initially and then the second eye to become involved in the ensuing 24 to 48 hours. Treatment focuses on symptomatic relief that can include lubricating eye drops or ointments, warm or cold compresses, or topical antihistamines. Topical antibiotic therapy has no role for a viral infection, and use of topical corticosteroid medication has no role in the treatment of viral conjunctivitis. These 2 therapies have been compared with the use of lubricating drops alone and have shown no greater benefit. Culture of the discharge is not needed. Even if this man's presentation was consistent with bacterial conjunctivitis, treatment with topical antibiotics is given without bacterial culture. In all cases of viral or bacterial conjunctivitis, patients should be advised that it is highly contagious and is spread by direct contact with secretions or with contaminated objects. Infected persons should not share handkerchiefs, tissues, towels, cosmetics, linens, or eating utensils. They should avoid touching their eyes and should wash their hands any time they do touch their eyes.

V.27. Answer c.

This patient does not have a written advance directive, but he has been clear with his family about his wishes. In this scenario, the family understands the prognosis and is able to clearly articulate what they believe the patient's values to be and how those values would most likely influence his preferences for care. Recommendations for a plan of care that is concordant with patient values is critically important in these situations and can help protect family members from feeling undue burden or that they are responsible for a patient's death. Although ethics consultation has been shown to help with conflict, it is not the best next step in this scenario. In addition, the family has already stated the patient's known preferences and indicated a desire to honor them; therefore they do not need to be reminded to do so. This family's challenge is with the surrogate decision-maker role, grief, and guilt. Acknowledging the difficulty of the scenario and scheduling a follow-up meeting is the second best option, and it may be a reasonable next step if the family needs more time after the clinician has made a recommendation.

V.28. Answer d.

This patient with severe, unrelenting pain is in a pain crisis, which requires urgent assessment and management, preferentially with intravenous opioids titrated to achieve improved pain control. The patient has chronic kidney disease, making hydromorphone and fentanyl the safest opioids for the acute management of her pain. Hydromorphone at 0.8 mg intravenously is approximately equianalgesic to the prior dose of oxycodone she received without effect, making it a safe starting point for managing her acute pain. A dose reduction when converting treatment between opioids is not applied in this case because her pain was unresponsive to initial treatment.

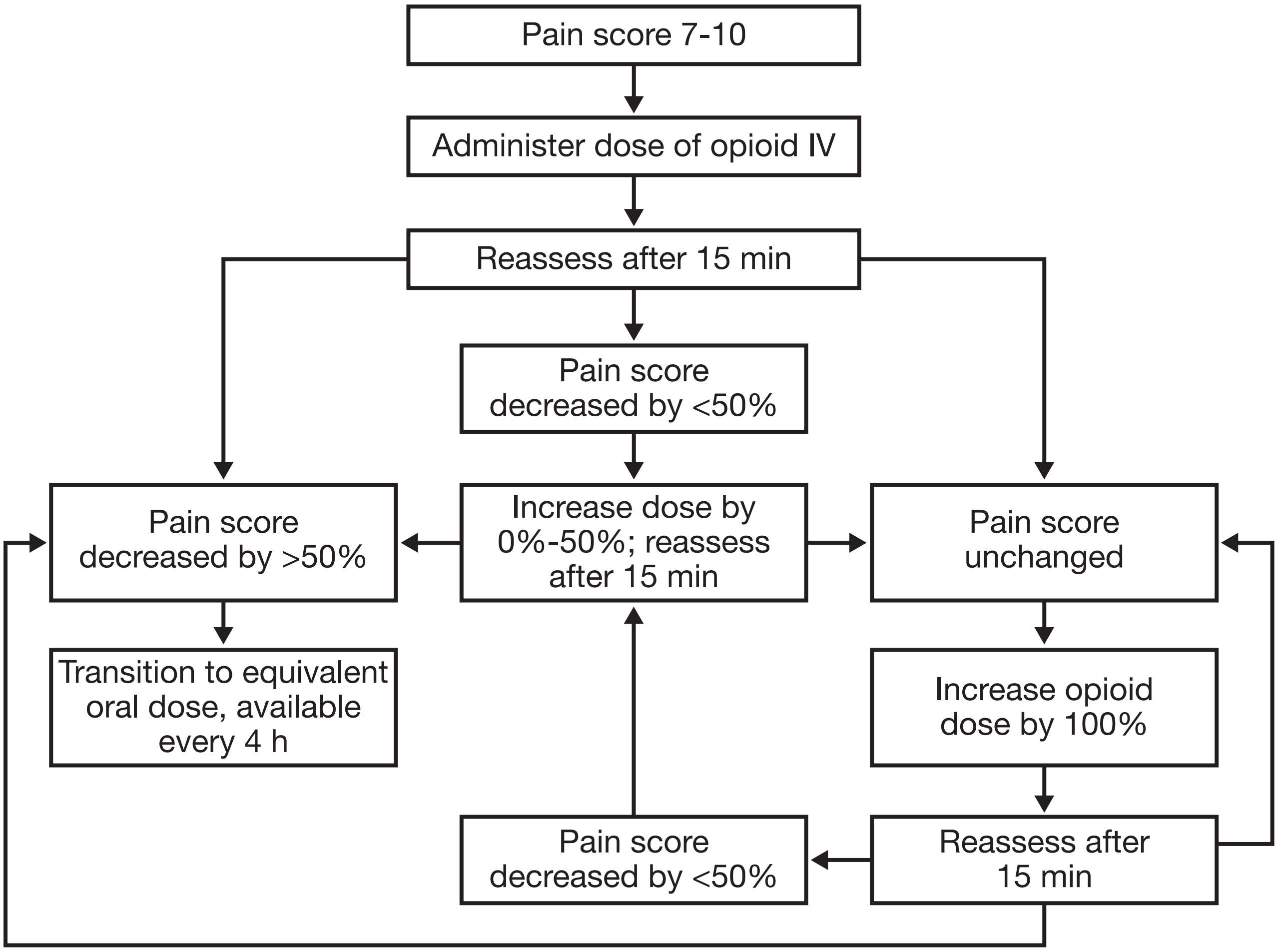
Pain score 7-10
Administer dose of opioid IV
Reassess after 15 min
Pain score decreased by <50%
Pain score decreased by >50%
Increase dose by 0%-50%; reassess after 15 min
Pain score unchanged
Transition to equivalent oral dose, available every 4 h
Increase opioid dose by 100%
Pain score decreased by <50%
Reassess after 15 min

Figure V.A28.

Ongoing titration of the intravenous dosing would be determined subsequently on the basis of how her pain responds to the initial dose (Figure V.A28). A higher dose of oral oxycodone will not allow for a quick initial response to her pain, and use of oral opiates will not allow for appropriately paced titration for a patient with a pain crisis. Oral hydromorphone may be a good choice in the future, after her pain crisis has resolved and her opiate needs are known. However, the 8-mg dose is too high for a starting point, on the basis of current information. Morphine is not recommended in the clinical setting of renal failure because of the accumulation of neurotoxic metabolites that cannot be removed in dialysis.

V.29. Answer b.

This patient has moderately severe cancer-associated pain that affects his ability to walk and care for himself. He has not received opiate therapy and tolerated gabapentin poorly. Given his advanced age and comorbidities, initiation of a trial of low-dose opioid, such as hydromorphone, on an intermittent and as-needed basis is a safe starting point for pain management. Tramadol is not the best choice for this patient with multiple comorbidities and advanced cancer because of a therapeutic ceiling effect, multiple drug-drug interactions that can result in increased risk of seizures and serotonin syndrome, and adverse effects similar to other, more potent opioids. Ibuprofen is a poor choice in this older patient with hypertension and chronic kidney disease because of his risk of worsening renal failure and gastrointestinal tract bleeding. A fentanyl patch is a poor choice at this time because we do not yet know the patient's response to opioids or opiate requirements. A fentanyl patch should only be used in opioid-tolerant patients after pain is stable and opiate requirements are known.

V.30. Answer b.

Burnout is a work-related syndrome of depersonalization, emotional exhaustion, and decreased sense of personal accomplishment. Although burnout may correlate with fatigue and other aspects of distress, including depression, it is a distinct set of felt experiences.

V.31. Answer c.

Physicians with burnout are more likely to reduce their FTE in the upcoming 12 to 24 months. Burnout is highly prevalent, with rates greater than 50% among US practicing physicians. Burnout is highest in "front-line" specialties, including internal medicine, family medicine, and emergency medicine. Solutions to burnout are a shared responsibility between the individual physician, health care organizations and institutions, and society.

V.32. Answer a.

Physician participation in small groups promotes interconnectedness and has been shown to reduce burnout. Although a change in specialty may provide a temporary solution for some physicians, it may not address the underlying cause and is not advisable when the current specialty reflects a long-desired goal. Increased work hours and reduced sleep time could potentially increase, rather than decrease, burnout.

V.33. Answer d.

This patient has multiple comorbidities contributing to elevated cardiac risk. Her Revised Cardiac Risk Index score is 3 (history of ischemic heart disease, type 2 diabetes mellitus requiring insulin therapy, and chronic kidney disease with creatinine >2 mg/dL), which corresponds to a 5.4% risk of a major adverse cardiac event. With application of the 2014 American College of Cardiology/American Heart Association perioperative cardiovascular evaluation algorithm (Figure V.A33), functional capacity should be considered for patients who are at elevated risk (>1%) for a major adverse cardiac event. Those who are asymptomatic and able to achieve 4 METS of activity or greater (as evidenced by this patient's ability to walk up a flight of stairs) may proceed to surgery without further cardiac testing. Therefore, the patient in this case needs no further cardiac testing, and echocardiography, exercise stress testing, and stress echocardiography are not indicated.

V.34. Answer b.

The American College of Cardiology/American Heart Association published an updated guideline in 2016 on antiplatelet therapy management for patients with coronary artery disease. This guideline addresses perioperative dual antiplatelet management in the clinical setting of newer-generation drug-eluting stents that confer a lower risk of stent thrombosis. Dual antiplatelet therapy can be interrupted (clopidogrel in this case may be held) for elective surgery at 6 months or later (class I recommendation). Aspirin therapy should be continued perioperatively unless the procedure-related bleeding risk is high, such as with central nervous system procedures.

V.35. Answer b.

The 2014 American College of Cardiology/American Heart Association (ACC/AHA) guideline on perioperative cardiovascular evaluation and care of patients undergoing noncardiac surgery recommends that patients who are currently taking a statin should continue to take it during the perioperative period. The guideline also states that it is reasonable to initiate a statin preoperatively for a patient undergoing vascular surgery. Studies have shown that the statins provide pleiotropic effects (such as anti-inflammatory properties, plaque stabilization, decreased activation of the blood coagulation cascade, and inhibition of platelet aggregation) that are independent of their cholesterol-lowering properties. Metoprolol treatment should be continued throughout the perioperative time frame according to the 2014 ACC/AHA guideline. Unless the bleeding risk is prohibitive, patients with history of coronary artery disease and cardiac stents should continue to take aspirin. α_2-Adrenergic agonists for prevention of cardiac events are not recommended for patients who are undergoing noncardiac surgery.

V.36. Answer b.

This patient should undergo colon cancer screening at age 40 years. According to the US Preventive Services Task Force, persons with a family history of colon cancer in a first-degree relative or in 2 second-degree relatives require a colonoscopy starting at age 40 or at 10 years before the youngest case in the immediate family, whichever is first. Colon cancer screening does not need immediate initiation because the patient is 38 years old and his father's colon cancer occurred at age 55. Initiating screening now would be reasonable if his father had colon cancer at age 48 or younger. Since the recommendations are 10 years before the youngest case in the immediate family or at age 40 years, whichever is first, this patient would not be screened at age 45 or 50. However, if he had no risk factors, screening would be recommended at age 50.

V.37. Answer c.

Because this patient's prior test was 3 years ago and she did not have an HPV cotest, the screening should happen now. In general, cervical cancer screening is recommended for women age 21 to 65 years. It can be performed by either Pap smear repeated every 3 years if results stay negative or Pap smear with HPV cotest every 5 years if results stay negative. If a woman has had routine screening with negative results, screening can be discontinued at age 65. However, this patient has only had 1 prior Pap smear; therefore, routine screening should be repeated before discontinuation of Pap smears. Additional sexually transmitted disease testing is not routinely recommended for women age 65 years and older, and therefore it is not recommended without additional information to indicate it is warranted.

V.38. Answer b.

This patient has completed his primary series of childhood vaccines. For his age group, recommended immunizations are a tetanus booster dose every 10 years and an annual influenza vaccine. His diagnosis of diabetes requires additional immunizations with hepatitis B and PPSV23 vaccines. No additional immunizations are recommended for the diagnosis of hyperlipidemia and hypertension, beyond the routine immunizations. This patient needs to complete the 3-dose hepatitis B series and receive a 1-time PPSV23 dose. PCV13 is recommended for all immunocompetent adults age 65 years and older. It is also indicated for adults younger than 65 who have certain conditions, including anatomic or functional asplenia, cerebrospinal fluid leak, cochlear implant, sickle cell disease, and specific immunocompromising conditions. PCV13 is not indicated in diabetes mellitus. Hepatitis A vaccination is recommended only for adults traveling to countries that have intermediate to high rates of endemic hepatitis A virus infection; adults caring for an international adoptee from a country with intermediate to high rates of endemic hepatitis A virus infection and within the first 60 days of the adoptee's arrival to the United States; persons with chronic liver disease; those receiving clotting factor concentrates; injection drug users; and men who have sex with men. Research personnel working in a laboratory where exposure to hepatitis A virus is a concern should also be vaccinated. This patient does not meet any of these criteria.

V.39. Answer a.

PDS A methods are widely used iterative methods in which a logical sequence of 4 repetitive steps are carried out over a course

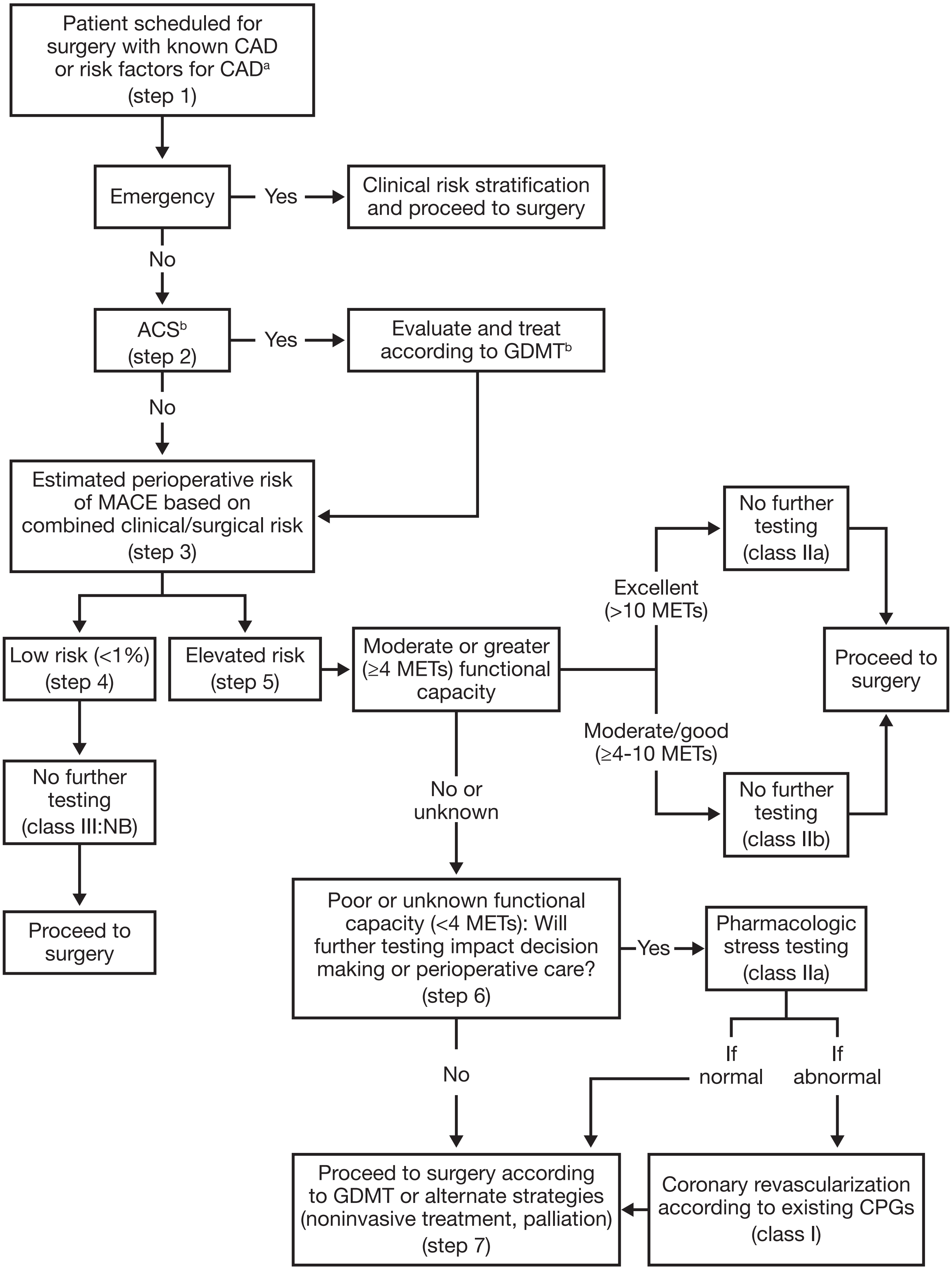
Patient scheduled for surgery with known CAD or risk factors for CAD^{a} (step 1)
Emergency
Yes
Clinical risk stratification and proceed to surgery
No
ACS^{b} (step 2)
Yes
Evaluate and treat according to GDMT^{b}
No
Estimated perioperative risk of MACE based on combined clinical/surgical risk (step 3)
Low risk (<1%) (step 4)
Elevated risk (step 5)
Moderate or greater (≥4 METs) functional capacity
Excellent (>10 METs)
No further testing (class IIa)
Proceed to surgery
Moderate/good (≥4-10 METs)
No further testing (class IIb)
No further testing (class III:NB)
Proceed to surgery
No or unknown
Poor or unknown functional capacity (<4 METs): Will further testing impact decision making or perioperative care? (step 6)
Yes
Pharmacologic stress testing (class IIa)
If normal
If abnormal
No
Proceed to surgery according to GDMT or alternate strategies (noninvasive treatment, palliation) (step 7)
Coronary revascularization according to existing CPGs (class I)

Figure V.A33.

of rapid, small cycles, eventually leading to exponential improvements. This would be an appropriate methodology to consider in addressing a complex problem such as medication reconciliation. Case management is a quality improvement approach used in managing special populations with a specific diagnosis and would not be appropriate for this type of problem. Benchmarking is a method of performance comparison against a broader standard; it is a quality improvement tool but not a methodology. Although computerized physician order entry implementation may be considered, it is a potential solution and not a methodology that allows a quality management reviewer to understand why the process performed poorly or why the reviewer would expect this proposed change to result in improvement.

V.40. Answer b.

Lean methodology is used to accelerate the velocity and reduce the cost of any process through the removal of waste. It would be an appropriate methodology for addressing inefficiencies in clinic flow. Process mapping and affinity diagramming are specific quality improvement tools that can be used, but they are not the broader methodologies that would help an improvement team comprehensively understand inefficiencies and determine the strategies to improve them. A failure mode effects analysis is a prospective review of vulnerabilities within a process, with the intent of safety event prevention. This tool is not generally used in projects with a primary aim of efficiency or flow improvement.

V.41. Answer c.

An understanding of the drivers of performance, relevant components of a future optimal state and the current state, and reasons for noted care gaps is foundational in guiding a successful improvement project. Without understanding of the underlying systems and processes, solutions are often misapplied or can serve to add confusion or complexity to the current state. Answer choices a, b, and d all propose solutions before engagement in the necessary work of understanding the process and the drivers for an observed care gap.

V.42. Answer c.

MHT is indicated for the treatment of bothersome vasomotor symptoms, including hot flushes and night sweats. Women may have bothersome symptoms during the perimenopausal period. If so, MHT not only is indicated but also is the most beneficial treatment. Although some data are suggestive that a reduction in coronary heart disease occurs with early initiation of hormone therapy, it is not indicated for primary prevention. Hormone therapy cannot be recommended at any age to prevent or treat dementia or a decline in cognitive function.

V.43. Answer b.

HPV vaccination is not recommended during pregnancy. The woman will need to wait until after her pregnancy to receive the HPV immunizations. Yet, she can be immunized against *Meningococcus*. Tdap is recommended during each pregnancy, ideally between 27 and 36 weeks' gestation.

V.44. Answer d.

Since the patient is older than 30 years, the next step in her evaluation is diagnostic left mammography and diagnostic ultrasonography. The description she provided is of pathologic nipple discharge—unilateral, spontaneous, and bloody—and requires further evaluation. In addition, although her mammogram was negative 7 months prior, she has dense tissue that can obscure abnormalities and her symptoms require further evaluation. MRI is a sensitive functional breast imaging study but has a high degree of false-positive results and is expensive. In addition, no data show a superiority of MRI over diagnostic mammography combined with diagnostic ultrasonography. At this point, MRI would not be advised for further evaluation. A referral to a surgeon for biopsy is premature at this point without any imaging. Although the most common cause of bloody nipple discharge is a benign intraductal papilloma, cancer must be considered, and it is appropriate to advise the patient that the possibility needs to be studied. A surgical referral would be reasonable to consider after breast imaging.

Section VI

Hematology

39

Benign Hematologic Disorders

NASEEMA GANGAT, MBBS

Anemias

Evaluation of Anemia

Anemia is a decrease in the mass of healthy circulating red blood cells (RBCs). It results from 1 of 3 mechanisms: 1) hypoproliferative anemia due to inadequate production of RBCs by the bone marrow (ie, marrow failure, intrinsic RBC synthetic defects, or lack of essential RBC components such as iron, vitamin B_{12}, or folate); 2) hyperproliferative anemia from blood loss; or 3) premature destruction of RBCs (ie, hemolysis). A complete history and physical examination should be performed; the mean corpuscular volume (MCV) then is used to classify anemia as microcytic, macrocytic, or normocytic.

Microcytic Anemias

Microcytic anemia indicates the presence of small RBCs (MCV <80 fL). The most common forms of anemia are microcytic (Tables 39.1 and 39.2). The causes of hypochromic microcytic anemias can be remembered with the mnemonic *TAILS* (thalassemia, anemia of chronic disease, iron deficiency, lead poisoning, and sideroblastic anemia).

A complete blood cell count and iron values (serum iron, total iron-binding capacity, transferrin saturation, and ferritin) aid in making a diagnosis (Table 39.2). Blood loss should be considered in all patients with microcytic anemia. Investigating the gastrointestinal tract (the most common site of occult blood loss) is essential in the work-up for microcytic anemia.

Iron Deficiency

Iron deficiency is the most common cause of anemia in the world and is especially common among menstruating or pregnant women and the elderly (Figure 39.1). Mechanisms of iron deficiency include 1) blood loss, 2) increased requirements (as in pregnancy), and 3) decreased absorption, including partial gastrectomy and malabsorption syndromes (eg, celiac disease).

Blood loss can occur in gastrointestinal tract disorders (eg, ulcers, cancer, telangiectasia, arteriovenous malformations, hiatal hernia, or long-distance runner's anemia); respiratory disorders (eg, cancer or pulmonary hemosiderosis); menstruation; phlebotomy (eg, blood donation, diagnostic phlebotomy, treatment of polycythemia vera or hemochromatosis, or self-inflicted or factitious injury); trauma; and surgery.

Patients may have a normal MCV if they have early iron deficiency or if they have a condition that causes macrocytosis (eg, iron deficiency in combination with folate deficiency).

The serum ferritin test is the most useful initial test for iron deficiency. A ferritin level less than 15 mcg/L almost always indicates iron deficiency. Ferritin is an acute phase protein, and the level is increased in inflammatory states. Thus, patients with such conditions may have iron deficiency even if the ferritin level is normal or increased. An increased level of soluble transferrin receptor (sTfR), which is not an acute phase protein, also signifies iron deficiency.

Oral iron replacement therapy is the treatment of choice for iron deficiency. Gastric acid is required for optimal iron absorption. Reticulocytosis is seen in 4 to 7 days after initiating oral iron replacement therapy, improvement in anemia in 3 to 4 weeks, and correction of anemia in 6 weeks. Iron replacement therapy should then be continued for another 6 months to replenish iron reserves. The main adverse effect of oral iron is gastrointestinal tract symptoms such as nausea, gastritis, and constipation.

Indications for intravenous iron therapy include hemodialysis (with recombinant erythropoietin) and inability to tolerate or absorb iron orally.

Thalassemias

The thalassemias are common single-gene disorders. β-Thalassemia results when β-globin chains are decreased or

Table 39.1 • Typical Features of Uncomplicated Microcytic Anemias (Decreased MCV)

	Type of Anemia	
Variable	**Thalassemia**	**Iron Deficiency**
RBC count, $\times 10^{12}$/L	≥5.0	<5.0
RBC distribution width, %	<16	≥16

Abbreviations: MCV, mean corpuscular volume; RBC, red blood cell.

absent in relation to α-globin. In α-thalassemia, the converse is true: Excess β-globin chains precipitate as tetramers called *hemoglobin H*. Genetic counseling is indicated after the diagnosis of α- or β-thalassemia has been established.

β-Thalassemia

Point mutations result in β-thalassemia of varying severity. Clinically, β-thalassemia is categorized as follows:

1. *β-Thalassemia trait*—microcytosis and either normal hemoglobin or mild anemia
2. *β-Thalassemia intermedia*—microcytosis and moderate anemia without long-term transfusion dependence
3. *β-Thalassemia major* (also known as Cooley anemia)—profound anemia and lifelong transfusion dependence.

In β-thalassemia, the hemoglobin A_2 level is increased (Figure 39.2). However, if the patient has iron deficiency, the hemoglobin A_2 level may be normal.

α-Thalassemia

Normally, a person has 4 α-globin genes but only 2 β-chain loci. α-Thalassemia is classified as follows:

1. *α-Thalassemia minor* (*α-thalassemia trait)*—absence of 1 or 2 of the 4 α-globin genes (patients are asymptomatic, usually with a low-normal MCV and normal hemoglobin level)
2. *Hemoglobin H disease*—absence of 3 α-globin genes (patients have chronic hemolytic anemia of moderate severity and may benefit from splenectomy if hemolysis becomes problematic)
3. Absence of all 4 α-globin genes is not compatible with life and results in stillbirth (hydrops fetalis).

KEY FACTS

✓ Microcytic anemia—most common form of anemia

✓ TAILS—mnemonic for causes of hypochromic microcytic anemia (thalassemia, anemia of chronic disease, iron deficiency, lead poisoning, and sideroblastic anemia)

✓ Early iron deficiency or macrocytosis—MCV may be normal

✓ Best initial test for iron deficiency—serum ferritin level (<15 mcg/L)

✓ Therapy for iron deficiency is oral iron—

- requires gastric acid for best absorption
- in 4-7 days: reticulocytosis
- in 3-4 weeks: improvement in anemia
- in 6 weeks: correction of anemia (continue iron for 6 more months to replenish reserves)

Macrocytic Anemias

Macrocytic anemia indicates the presence of large RBCs (MCV >100 fL). The differential diagnosis of macrocytic anemias includes vitamin B_{12} deficiency, folate deficiency, use of certain drugs, liver disease, alcohol abuse, hypothyroidism, heavy tobacco use, myelodysplasia or other primary bone marrow disorders, cold agglutinin disease (artifactual clumping of cells in an automated counter), and reticulocytosis (reticulocytes are larger than mature RBCs). A laboratory approach to characterization of macrocytic anemias is shown in Figure 39.3. An MCV greater than 115 fL almost always indicates a

Table 39.2 • Comparison of the Most Common Hypochromic Microcytic Anemias

Disease State	**MCV**	**Red Blood Cell Count**	**TIBC**	**Transferrin Saturation**	**Serum Ferritin**	**Marrow Iron**
Iron deficiency anemia	Decreased	Decreased	Increased	Low	Low	Absent
Anemia of chronic disease	Normal or decreased	Decreased	Normal or low	Normal or increased	Normal or increased	Normal or increased
Thalassemia minor	Decreased	Usually increased	Normal	Normal	Normal or increased	Normal

Abbreviations: MCV, mean corpuscular volume; TIBC, total iron-binding capacity.

Modified from Savage RA. Cost-effective laboratory diagnosis of microcytic anemias of complex origin. ASCP check sample H84-10(H-153); used with permission.

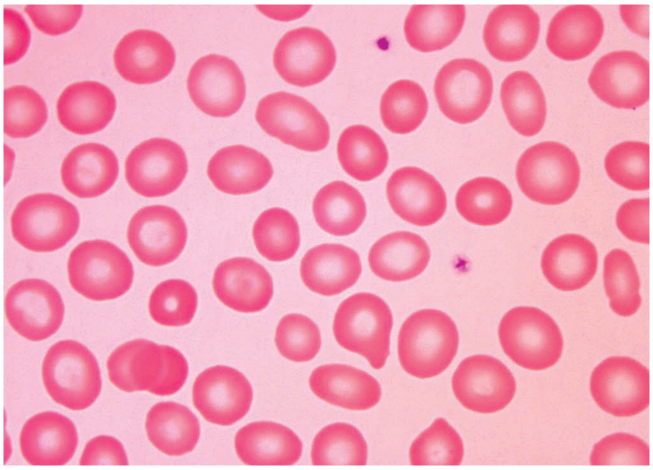

Figure 39.1. *Hypochromic Microcytic Anemia. The erythrocytes are small with increased central pallor and assorted aberrations in size (anisocytosis) and shape (poikilocytosis). This pattern is characteristic of iron deficiency rather than thalassemia; in thalassemia, red blood cells are small but more uniform. If a mature lymphocyte is available for reference, the diameter of a normal erythrocyte (7 mcm) should be similar to the diameter of the nucleus of the lymphocyte (peripheral blood smear; Wright-Giemsa).*

(Courtesy of Curtis A. Hanson, MD, Mayo Clinic, Rochester, Minnesota; used with permission.)

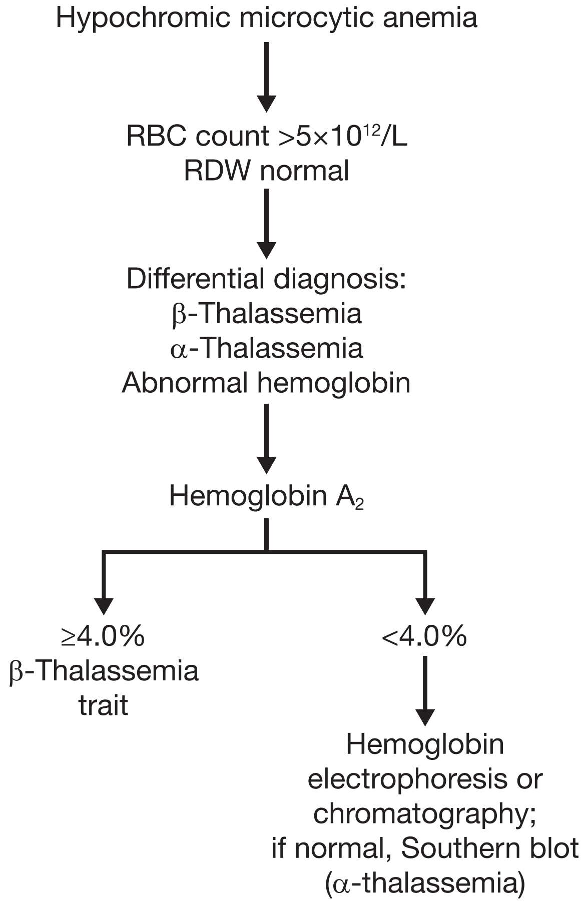

Figure 39.2. *Algorithm for Approach to Diagnosis of Hypochromic Microcytic Anemia With an Increased Total Red Blood Cell (RBC) Count and a Normal RBC Distribution Width (RDW).*

(Modified from Savage RA. Cost-effective laboratory diagnosis of microcytic anemias of complex origin. ASCP check sample H84-10[H-153]; used with permission.)

deficiency of either vitamin B_{12} or folate or an artifact due to RBC agglutination. Common drug-related causes of macrocytosis are chemotherapy drugs that inhibit purine or pyrimidine synthesis (eg, azathioprine or 5-fluorouracil), deoxyribonucleotide synthesis (hydroxyurea or cytarabine), or dihydrofolate reductase (methotrexate).

Vitamin B_{12} Deficiency

Vitamin B_{12} (cobalamin) is present mainly in animal products. Hydrochloric acid is necessary to free cobalamin from food. Free cobalamin is immediately bound by R-binders, which protect cobalamin from the acidic gastric environment. As the complex passes into the duodenum, pancreatic proteases facilitate release of the R-binders. The free cobalamin then combines with intrinsic factor and is absorbed in the terminal ileum.

Vitamin B_{12} deficiency due to inadequate dietary intake is rare (seen usually in strict vegetarians). Causes of vitamin B_{12} deficiency include pernicious anemia (defective production of intrinsic factor, due to anti–intrinsic factor or anti–parietal cell antibodies), atrophic gastritis, total or partial gastrectomy, ileal resection or Crohn disease involving the ileum, bacterial overgrowth syndromes, infection with *Diphyllobothrium latum*, and exocrine pancreatic insufficiency. Prolonged metformin use has also been described as a cause of vitamin B_{12} deficiency.

The symptoms and signs of vitamin B_{12} deficiency include a beefy and atrophic tongue, diarrhea, and neurologic signs (eg, paresthesias, gait disturbance, mental status changes ["B_{12} madness"], vibratory/position sense impairment [dorsal column "dropout"], the absence of ankle reflexes, and extensor plantar responses).

The MCV is increased, and hypersegmented neutrophils are usually present (Figure 39.4). As in folate deficiency, serum homocysteine levels are increased; however, unlike in folate deficiency, serum and urinary levels of methylmalonic acid are also increased. A serum vitamin B_{12} level less than 200 ng/L strongly suggests vitamin B_{12} deficiency. Vitamin B_{12} levels of 200 to 400 ng/L (borderline or low-normal range) can also indicate deficiency; if clinical suspicion is high, methylmalonic acid levels can help establish the diagnosis. When present, an abnormal intrinsic factor antibody confirms pernicious anemia as the cause of vitamin B_{12} deficiency.

Vitamin B_{12} deficiency, including pernicious anemia, is treated with oral or intramuscular vitamin B_{12}. Lifelong maintenance treatment is required.

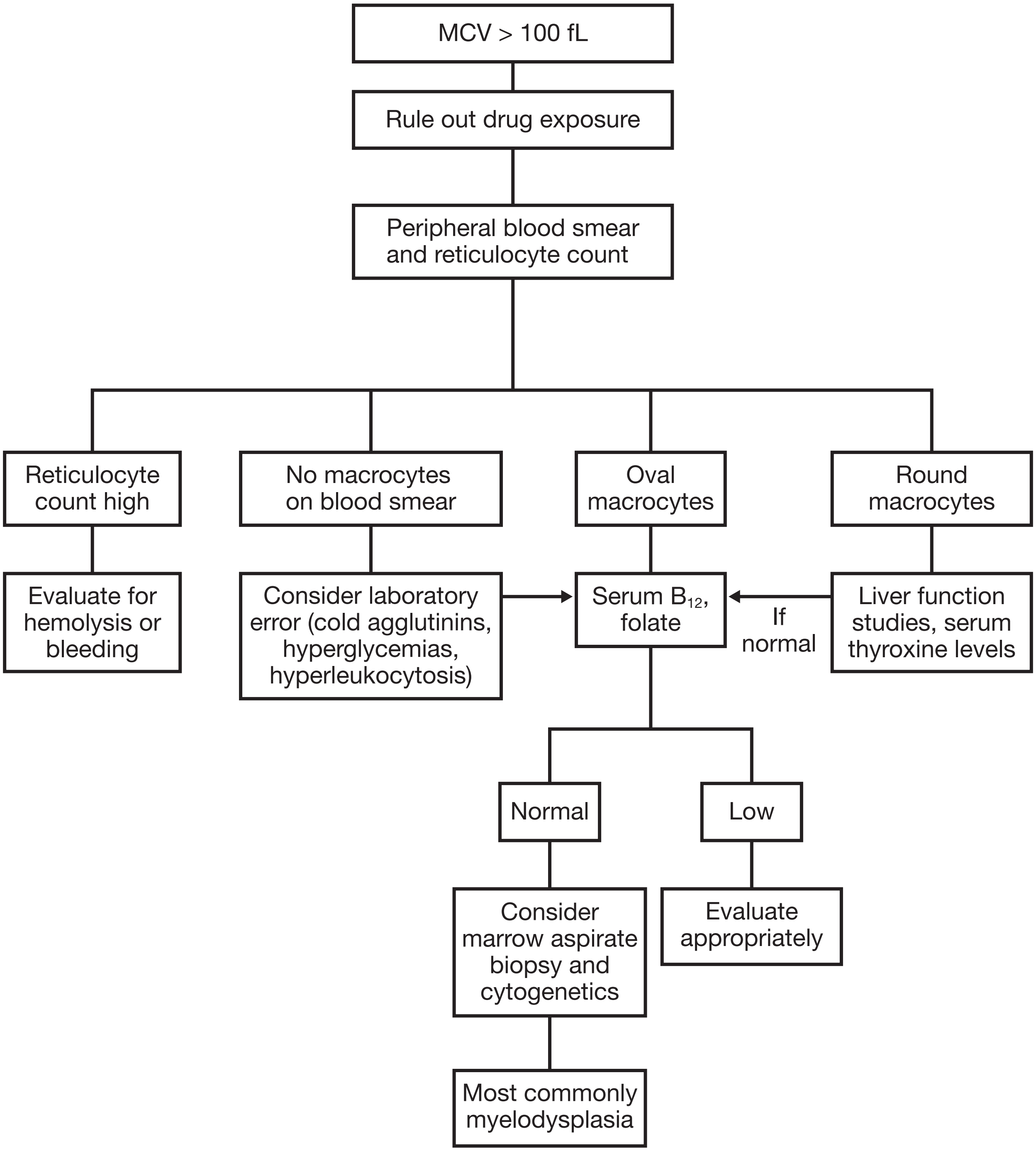
MCV > 100 fL
Rule out drug exposure
Peripheral blood smear and reticulocyte count
Reticulocyte count high
No macrocytes on blood smear
Oval macrocytes
Round macrocytes
Evaluate for hemolysis or bleeding
Consider laboratory error (cold agglutinins, hyperglycemias, hyperleukocytosis)
Serum B12, folate
If normal
Liver function studies, serum thyroxine levels
Normal
Low
Consider marrow aspirate biopsy and cytogenetics
Evaluate appropriately
Most commonly myelodysplasia

Figure 39.3. Laboratory Approach to Characterization of Macrocytic Anemias. MCV indicates mean corpuscular volume.

(From Colon-Otero G, Menke D, Hook CC. A practical approach to the differential diagnosis and evaluation of the adult patient with macrocytic anemia. Med Clin North Am. 1992 May;76[3]:581-97; used with permission.)

Folate Deficiency

In contrast to anemia caused by vitamin B_{12} deficiency, macrocytic anemia caused by folate deficiency develops quickly (ie, within months) in patients with inadequate dietary intake of folic acid. Folate is present in green leafy vegetables, and many foods are fortified with folate in most Western countries. It is absorbed in the duodenum and proximal jejunum. Mechanisms of folate deficiency include 1) increased requirements (eg, pregnancy or hemolytic anemia); 2) poor folate intake (eg, alcoholism or malnutrition); 3) poor absorption (eg, celiac disease, bariatric surgery, or drugs that interfere with absorption, such as phenytoin, phenobarbital, and primidone); and 4) interference with the recycling of folate from liver stores to tissue (eg, alcohol).

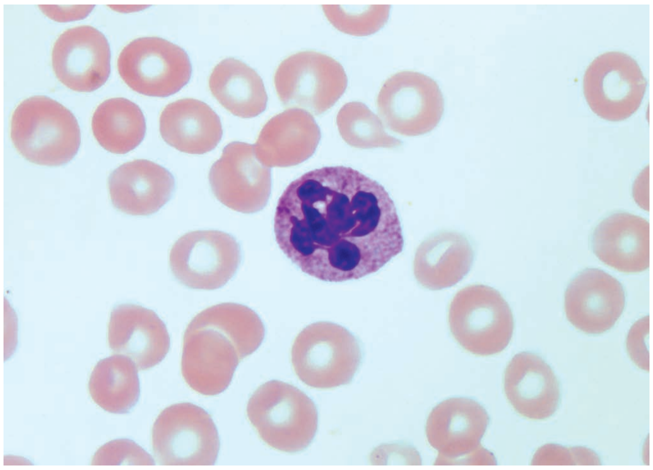

Figure 39.4. *Hypersegmented Neutrophil.* *Polymorphonuclear leukocytes with 5 or more nuclear lobes are characteristic of vitamin B_{12} or folate deficiency and are not typically seen in other causes of macrocytic anemia (peripheral blood smear; Wright-Giemsa).*

The possibility of coexistent vitamin B_{12} or iron deficiency should be considered if the response to replacement folate therapy is not optimal. Folate helps convert homocysteine to methionine; thus, folate deficiency leads to an increased homocysteine level. In contrast to vitamin B_{12} deficiency, in folate deficiency the level of methylmalonic acid is normal.

Normocytic Anemias

Differential Diagnosis

Normocytic anemia is defined as anemia with an MCV of 80 to 100 fL. The differential diagnosis includes mixed nutritional deficiency (eg, concomitant folate and iron deficiency), erythropoietic failure (aplastic anemia or pure RBC aplasia), marrow replacement (malignant process or fibrosis), kidney disease with lack of erythropoietin production, hemolysis, acute hemorrhage, chemotherapy, anemia of acute disease, and anemia of chronic disease (ACD) (eg, infections, neoplasia, rheumatoid arthritis, or other inflammatory rheumatologic conditions).

Key Definitions

Anemia: *reduced mass of healthy circulating RBCs.*
Microcytic anemia: *MCV <80 fL.*
Macrocytic anemia: *MCV >100 fL.*
Normocytic anemia: *MCV 80-100 fL.*

Anemia of Chronic Disease

In ACD, the anemia is usually moderate (ie, hemoglobin value, 9-11 g/dL), MCV is normal or modestly decreased, and the reticulocyte count is low. ACD is sometimes called anemia of chronic inflammation, because it results from the inhibitory effects of inflammatory cytokines on the bone marrow. A peptide produced by the liver, hepcidin, is increased in ACD. Hepcidin sequesters iron and decreases iron absorption. As a consequence, serum iron levels are low in ACD, but unlike in iron deficiency, total iron-binding capacity is normal or low and the ferritin level is usually normal or increased (Table 39.2).

Early in the evaluation of patients with suspected ACD, it is important to exclude hemolysis and gastrointestinal tract blood loss. No single blood test confirms ACD, but the diagnosis is probable if 1) inflammatory markers are present; 2) results of iron studies are typical (ie, normal total iron-binding capacity, normal or increased serum ferritin level, and normal or increased transferrin saturation); 3) another cause for the normocytic anemia is not apparent; and 4) the clinical setting is appropriate. The sTfR concentration is normal in ACD in contrast to iron deficiency anemia, in which sTfR is usually increased. Patients with ACD do not benefit from iron therapy. Patients with ACD resulting from chronic kidney disease benefit from administration of erythropoietin.

Sideroblastic Anemias

The sideroblastic anemias are characterized by microcytic, normocytic, or macrocytic anemia and ring sideroblasts in the bone marrow (Figure 39.5). Ring sideroblasts are abnormal erythroid precursors ineffective at heme synthesis and are often seen in myelodysplastic syndromes. Reactive causes include alcohol, zinc toxicity, and drugs such as isoniazid and pyrazinamide. Several forms of congenital sideroblastic anemia respond to vitamin B_6 (pyridoxine) therapy.

Aplastic Anemia

Aplastic anemia is a hematopoietic stem cell disorder characterized by pancytopenia, bone marrow hypocellularity, and absence of another disorder that would explain the hypocellularity (eg, myelodysplastic syndrome, T-cell clonal disorders, or other congenital bone marrow failure syndromes). Acquired aplastic anemia is often idiopathic. Common causes include drugs (eg, chloramphenicol, sulfonamides, gold, or benzene), toxins, radiation, viral infections (eg, hepatitis A virus, Epstein-Barr virus [EBV], cytomegalovirus, human immunodeficiency virus [HIV], or human parvovirus B19), and autoimmune marrow suppression. The criteria for severe aplastic anemia include less than 25% of expected marrow cellularity and 2 of the following: 1) neutrophil count less than 0.5×10^9/L; 2) platelet count less than 20×10^9/L; and 3) a corrected reticulocyte count less than 1%.

Allogeneic hematopoietic stem cell transplant is the therapy of choice for patients with an identical twin, for patients younger than 20 years, or for high-risk patients aged 20 to 40 years who have an HLA match. For patients older than 40 years, the treatment of choice is antithymocyte globulin in combination with corticosteroids and cyclosporine. The thrombopoietin receptor analog eltrombopag is indicated for patients with severe aplastic anemia who do not respond adequately to immunosuppressive

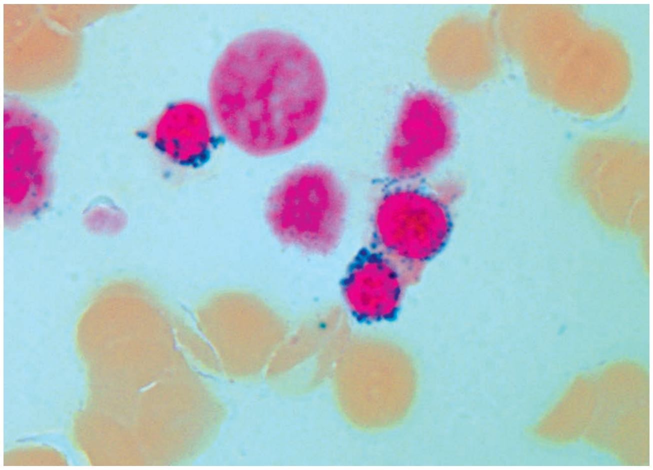

Figure 39.5. *Ring Sideroblasts. Seen on iron staining of bone marrow aspirate, ring sideroblasts can be reactive, congenital, or part of a myelodysplastic syndrome or other clonal myeloid disorder (bone marrow aspirate; iron stain with potassium ferrocyanide and nuclear fast red counterstain).*

(Courtesy of Curtis A. Hanson, MD, Mayo Clinic, Rochester, Minnesota; used with permission.)

therapy. Without treatment, 80% of patients who have severe aplastic anemia die within 2 years after receiving the diagnosis.

KEY FACTS

- ✓ Macrocytic anemia differential diagnosis—vitamin B_{12} or folate deficiency, drugs (including alcohol and tobacco), liver disease, hypothyroidism, primary bone marrow disorders, cold agglutinin disease, and reticulocytosis
- ✓ Vitamin B_{12} deficiency—
  - increased serum homocysteine level (like in folate deficiency)
  - increased serum and urinary methylmalonic acid levels (unlike in folate deficiency)
  - strongly suggested by serum vitamin B_{12} level <200 ng/L
  - may be indicated by serum vitamin B_{12} level 200-400 ng/L
  - if clinical suspicion is high, check methylmalonic acid level
- ✓ Anemia of chronic disease—
  - decreased serum iron level (like in iron deficiency)
  - normal or low total iron-binding capacity (unlike in iron deficiency)
  - normal or increased ferritin level

Sickle Cell Disorders

Classification and Pathophysiology

The sickle cell disorders include sickle cell anemia (homozygous hemoglobin S), sickle cell trait (heterozygous hemoglobin S), and compound states (hemoglobin S with thalassemia or other hemoglobinopathies).

Sickle cell disorders occur in persons of sub-Saharan African descent: Approximately 1 of every 8 African Americans carries 1 copy of the sickle cell gene, and sickle cell disease occurs in 1 of 500. Hemoglobin S substitutes valine for glutamic acid at the sixth position of the β chain. Deoxygenated hemoglobin S distorts the cell into a sickle shape and injures the cell membrane (Figure 39.6). Sickling is inhibited by hemoglobin F; therefore, symptoms are not apparent until after 6 months of age. Acute chest syndrome is the leading cause of death (25% of deaths) in sickle cell anemia; clinical features include fever, chest pain, tachypnea, leukocytosis, and pulmonary infiltrates. Infection is usually caused by pneumococci, *Mycoplasma, Haemophilus, Salmonella*, or *Escherichia coli*. Aplastic crises are often associated with human parvovirus B19 infection. Osteomyelitis is caused by *Salmonella, Staphylococcus*, or pneumococci. Acute and chronic complications of sickle cell anemia are summarized in Box 39.1.

Laboratory findings include severe anemia (hemoglobin, 5.5-9.5 g/dL), sickled cells, ovalocytes, target cells, basophilic stippling, polychromatophilia, reticulocytosis (3%-12%), and hyposplenia with Howell-Jolly bodies (Figure 39.7). A persistent increase in the white blood cell count to 12×10^9/L to 15×10^9/L (in the absence of infection) with eosinophilia is characteristic. Evidence of chronic hemolysis may be present. Routine diagnostic tests include the sickle solubility test, electrophoresis, and chromatography.

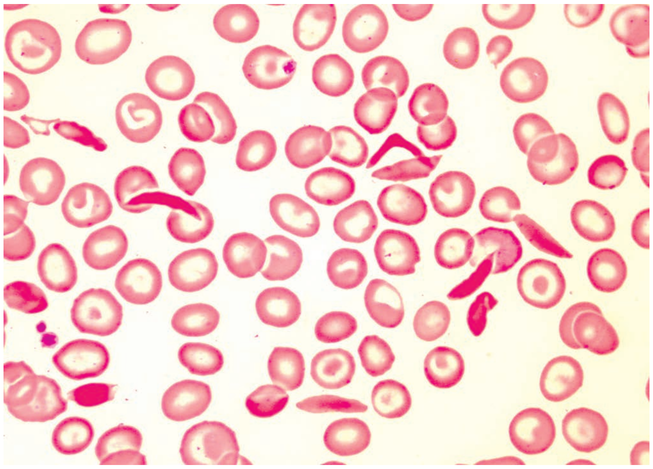

Figure 39.6. *Sickle Cell Anemia. This photomicrograph shows several irreversibly sickled cells. Abundant target cells indicate hyposplenism from autoinfarction of the spleen. Liver disease due to transfusional hemosiderosis was also a contributing factor to these target cells (peripheral blood smear; Wright-Giemsa).*

Box 39.1 • Complications and Treatment of Sickle Cell Anemia

- Acute complications
  - Vasoocclusive episodes
  - Acute chest syndrome
  - Dactylitis
  - Splenic sequestration
  - Stroke
  - Aplastic crisis
  - Infection
  - Acute cholecystitis
  - Priapism
  - Renal papillary necrosis
- Chronic complications
  - Hemolytic anemia
  - Growth retardation
  - Pulmonary hypertension
  - Folate deficiency
  - Retinopathy
  - Chronic renal insufficiency
  - Accelerated cardiovascular disease
  - Transfusional hemochromatosis
  - Nonhealing skin ulcers
  - Osteopenia
  - Avascular necrosis
- Treatment
  - Pain crises: gentle hydration and pain control
  - Stroke, acute chest syndrome, priapism, progressive retinopathy: exchange transfusion with goal hemoglobin S <30%

Treatment

Sickle cell crises can be prevented by avoiding infection, fever, dehydration, acidosis, hypoxemia, cold, and high altitude. Most patients with sickle cell disease undergo autosplenectomy through recurrent infarction by age 5 years. Immunizations for encapsulated organisms, penicillin prophylaxis, and folate supplementation are indicated. Treatment of complications is summarized in Box 39.1.

Treatment with hydroxyurea decreases the frequency of painful vasoocclusive crises (by about 50%) and acute chest syndrome and the number of transfusions and hospitalizations. It is indicated for patients who have had severe complications such as acute chest syndrome and frequent, painful crises.

Hematopoietic stem cell transplant with marrow or umbilical cord blood from HLA-identical siblings may be curative. Indications for transplant include stroke and recurrent acute chest syndrome.

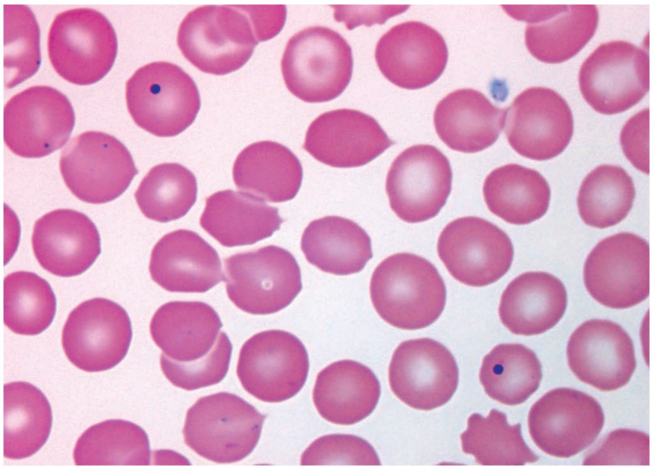

Figure 39.7. *Howell-Jolly Bodies. These small, round blue inclusions are seen with Wright-Giemsa or a comparable stain. They are characteristic of hyposplenism due to splenectomy or to a functionally defective spleen. Howell-Jolly bodies should not be confused with Heinz bodies, which require a special Heinz body preparation to observe and are not seen on a conventional peripheral smear (peripheral blood smear; Wright-Giemsa).*

Sickle Cell Trait and Compound States

Sickle cell trait (heterozygous hemoglobin S) is not associated with anemia, RBC abnormalities, increased risk of infections, or increased risk of death. Sickle cell trait is associated with hematuria due to renal papillary necrosis, splenic infarction at high altitude (>3,000 m), hyposthenuria, pyelonephritis in pregnancy, and pulmonary embolism. Compound states such as sickle cell–hemoglobin C disease and hemoglobin S/β-thalassemia are generally milder than sickle cell disease, depending on the hemoglobin concentrations.

Hemolytic Anemias

Findings and Diagnosis

Hemolysis is the premature destruction of RBCs. If hemolytic anemia is suspected, the first step is to confirm the presence of hemolysis. Hemolytic anemias are characterized by increased RBC destruction and increased RBC production (Box 39.2).

Peripheral blood smear findings can assist in making a diagnosis. Each finding in the following list suggests various possible causes:

- *Spherocytes* (Figure 39.8)—hereditary spherocytosis, alcohol abuse, autoimmune hemolytic anemia
- *Basophilic stippling*—lead poisoning, β-thalassemia, arsenic poisoning
- *Hypochromia*—thalassemia, sideroblastic anemia, lead poisoning
- *Target cells* (Figure 39.9)—thalassemia, liver disease, previous splenectomy

Box 39.2 • Characterization of Hemolytic Anemia

- Increased red blood cell (RBC) destruction
  - Increased indirect bilirubin level (>8 mg/dL suggests concomitant liver disease)
  - Increased lactate dehydrogenase level
  - Decreased haptoglobin level (haptoglobin, a scavenger of free hemoglobin, may be transiently decreased after transfusion or hemodialysis)
- Increased RBC production
  - Increased reticulocyte count
  - Marrow erythroid hyperplasia

- *Agglutination* (Figure 39.10)—cold agglutinin disease
- *Stomatocytes*—acute alcoholism, artifact
- *Spur cells* (*acanthocytes*) (Figure 39.11)—chronic severe liver disease, abetalipoproteinemia, malabsorption
- *Burr cells* (*echinocytes*) (Figure 39.12)—uremia, but disappearing with hemodialysis
- *Heinz bodies*—glucose-6-phosphate dehydrogenase (G6PD) deficiency (seen with supravital staining)
- *Howell-Jolly bodies* (Figure 39.7)—hyposplenism
- *Polychromasia* (Figure 39.13)—reticulocytosis
- *Intraerythrocytic parasitic inclusions* (Figure 39.14)—malaria, babesiosis

Hemolytic anemias may result from factors that are intrinsic or extrinsic to the RBC and may have negative or positive results of the direct antiglobulin test (DAT), also called the direct Coombs test (Figure 39.15). A positive DAT result indicates the presence of complement component C3 or immunoglobulin (Ig) G (or both) on the surface of RBCs. Notably, an aplastic crisis may occur in chronic hemolytic anemia and usually results from folate deficiency or parvovirus infection.

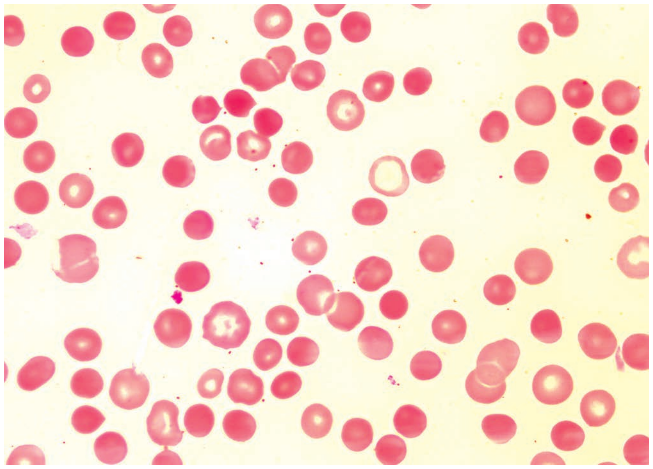

Figure 39.8. *Spherocytes. Spherocytes are the smooth, small, and spheroidal darkly stained cells with minimal or no central pallor. They are most commonly seen in hereditary spherocytosis or autoimmune hemolytic anemia (peripheral blood smear; Wright-Giemsa).*

(Courtesy of Curtis A. Hanson, MD, Mayo Clinic, Rochester, Minnesota; used with permission.)

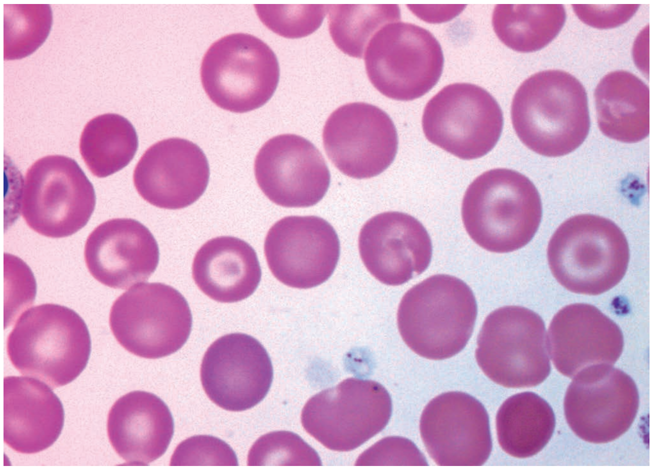

Figure 39.9. *Target Cells. Target cells are red blood cells with a broad diameter and dark center with a pale surrounding halo. They are most commonly seen in hemoglobin C disease, thalassemia, and liver disease and after splenectomy (peripheral blood smear; Wright-Giemsa).*

(Courtesy of Curtis A. Hanson, MD, Mayo Clinic, Rochester, Minnesota; used with permission.)

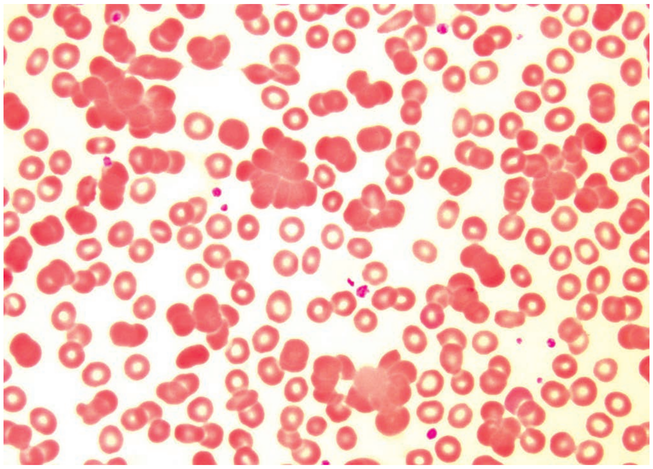

Figure 39.10. *Agglutination. The random clumping of red blood cells most commonly indicates cold agglutinin disease or laboratory artifact. It is important to distinguish agglutination from rouleaux (Figure 39.16) (peripheral blood smear; Wright-Giemsa).*

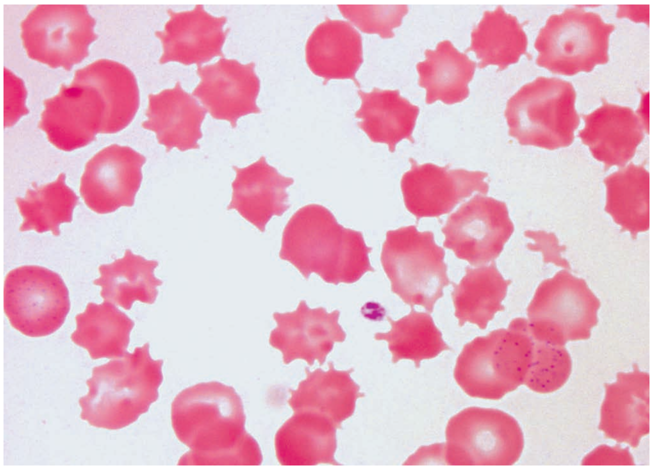

Figure 39.11. *Spur Cells (Acanthocytes). Note the thin, thorny, or fingerlike projections. Spur cells are characteristic of advanced liver disease and must be distinguished from burr cells (echinocytes) (Figure 39.12) (peripheral blood smear; Wright-Giemsa).* (Courtesy of Curtis A. Hanson, MD, Mayo Clinic, Rochester, Minnesota; used with permission.)

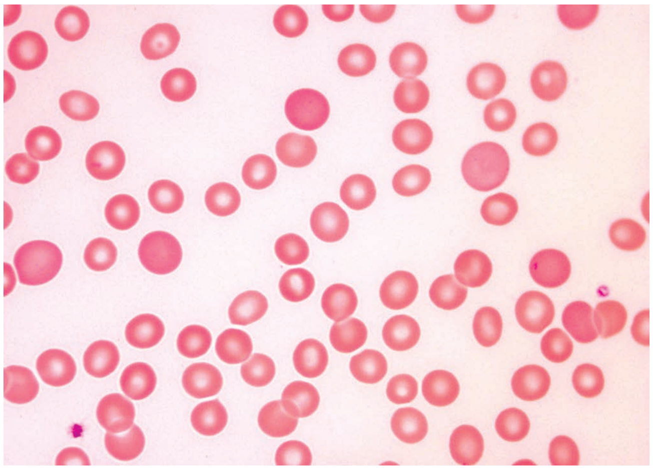

Figure 39.13. *Polychromasia. The larger cells are reticulocytes. These are often seen in high numbers during recovery from blood loss or hemolysis (peripheral blood smear; Wright-Giemsa).*

Intravascular Hemolysis Compared With Extravascular Hemolysis

In **intravascular hemolysis**, RBCs are destroyed while circulating within blood vessels. Their destruction releases free hemoglobin into the bloodstream, leading to hemoglobinemia, hemoglobinuria, and hemosiderinuria, all of which occur exclusively with intravascular hemolysis. Hemosiderinuria indicates that desquamated renal tubular cells absorbed free hemoglobin days to weeks earlier. Causes of intravascular hemolysis include transfusion reactions from ABO blood group antibodies, microangiopathic hemolytic anemia, paroxysmal nocturnal hemoglobinuria, paroxysmal cold hemoglobinuria, cold agglutinin syndrome, immune-complex drug-induced hemolytic anemia, infections (including falciparum malaria and clostridial sepsis), and G6PD deficiency. All other forms of hemolysis are primarily **extravascular hemolysis**, in which the RBCs are lysed in the macrophages of the spleen and liver.

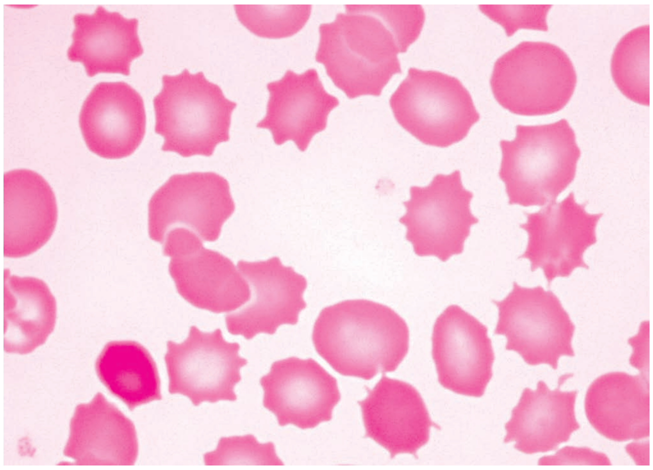

Figure 39.12. *Burr Cells (Echinocytes). Burr cell projections are much smaller and more uniform in size than spur cell projections. Burr cells are characteristic of uremia, and the membrane abnormality is reversible with hemodialysis (peripheral blood smear; Wright-Giemsa).*

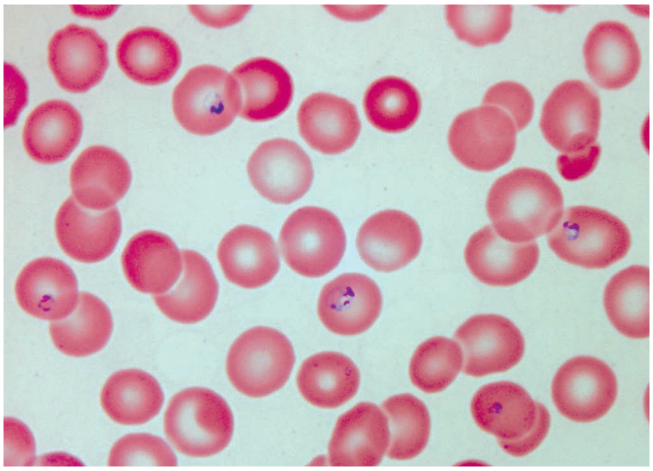

Figure 39.14. *Intraerythrocytic Ring-Shaped Parasites of Babesiosis. Malaria is the other common disease with an intraerythrocytic parasite (peripheral blood smear; Wright-Giemsa).*

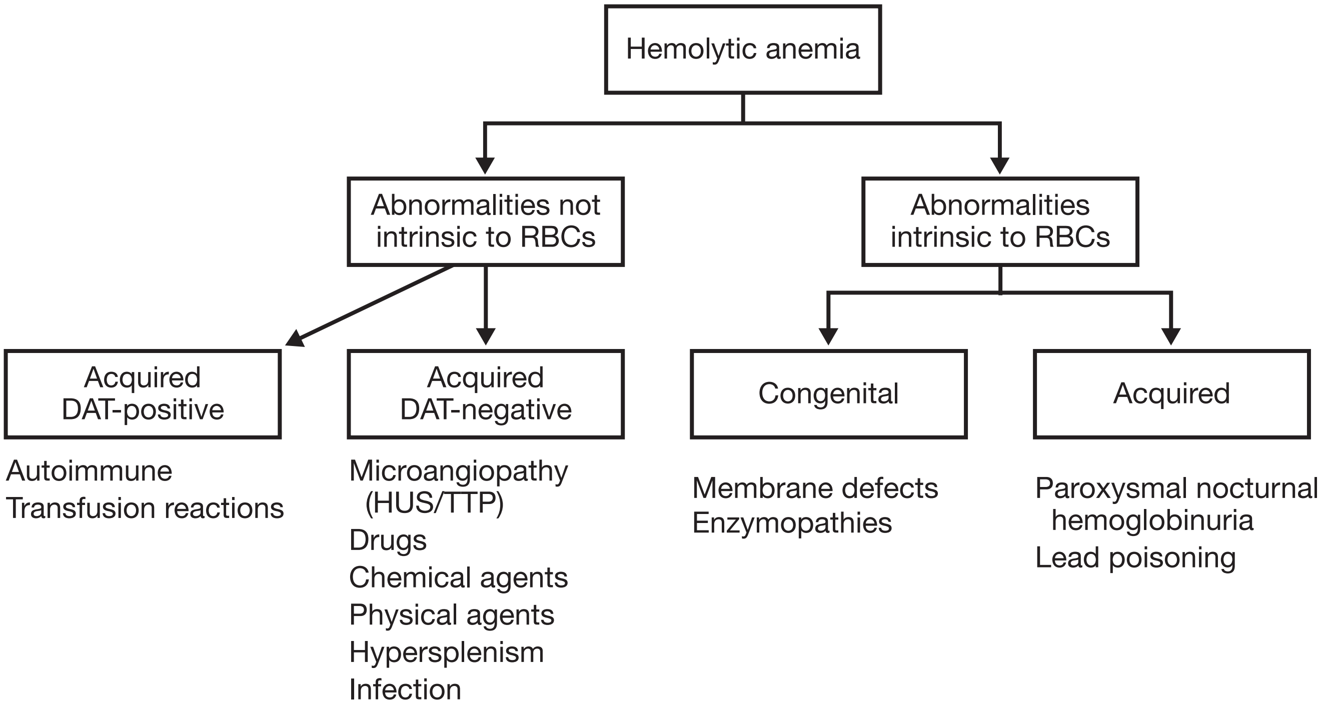
Hemolytic anemia
Abnormalities not intrinsic to RBCs
Abnormalities intrinsic to RBCs
Acquired DAT-positive
Acquired DAT-negative
Congenital
Acquired
Autoimmune
Transfusion reactions
Microangiopathy (HUS/TTP)
Drugs
Chemical agents
Physical agents
Hypersplenism
Infection
Membrane defects
Enzymopathies
Paroxysmal nocturnal hemoglobinuria
Lead poisoning

Figure 39.15. *Differential Diagnosis of Hemolytic Anemia. DAT indicates direct antiglobulin test; HUS, hemolytic uremic syndrome; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura.*

Key Definitions

Hemolysis: *premature destruction of RBCs.*

Intravascular hemolysis: *destruction of RBCs circulating within blood vessels.*

Extravascular hemolysis: *destruction of RBCs in macrophages of spleen and liver.*

Autoimmune Hemolytic Anemia

Drug-Induced Hemolytic Anemia

Hemolytic anemia may be drug induced, for which there are 3 distinct mechanisms. In the *autoantibody mechanism*, methyldopa may form autoantibodies that can induce hemolysis. DAT results are positive in 3 to 6 months. Discontinuing the use of methyldopa usually leads to a rapid reversal in hemolysis.

In the *drug adsorption mechanism*, the use of high doses of penicillins or cephalosporins for more than 7 days may lead to immunohemolytic anemia due to antibodies formed against the drug–RBC membrane antigen complex. In 3% of patients, the DAT is positive.

In the *immune complex mechanism*, exposure to quinidine may cause an antidrug antibody to form and create an immune complex, which is adsorbed on the RBCs and may activate complement. The DAT is positive because of the complement on the RBC surface.

Cold Agglutinin Syndrome (Primary Cold Agglutinin Disease)

Cold agglutinin syndrome is characterized by chronic hemolytic anemia, agglutination, and a positive DAT result (anti–complement component C3). IgM autoantibodies are reactive at temperatures below 37°C. The cause is most commonly idiopathic but can also be secondary to infection (most commonly from *Mycoplasma pneumoniae* or EBV) or a malignant process (B-cell lymphoma, chronic lymphocytic leukemia, multiple myeloma, or Waldenström macroglobulinemia). Clinical signs and symptoms relate to small-vessel occlusion, including acrocyanosis of the fingers, toes, ears, and tip of the nose.

The peripheral blood smear shows RBC agglutination that disappears if prepared at 37°C (Figure 39.10). Agglutinated RBCs clump together, which spuriously increases the MCV. Therapy includes avoidance of the cold. In severe cases, rituximab and cytotoxic agents are used. Agglutination should not be confused with rouleaux, in which RBCs stack in a linear pattern (Figure 39.16).

Warm Agglutinin Autoimmune Hemolytic Anemia

Warm agglutinins are IgG antibodies that bind to RBCs at physiologic temperatures rather than primarily in the cold. The DAT is positive for both IgG and complement component C3. Associated causes include autoimmune disorders (systemic lupus erythematosus), lymphoproliferative disorders (chronic lymphocytic leukemia), drugs, and transfusion. The first general principle in the treatment of warm agglutinin autoimmune hemolytic anemia is to treat the underlying disease (if one can

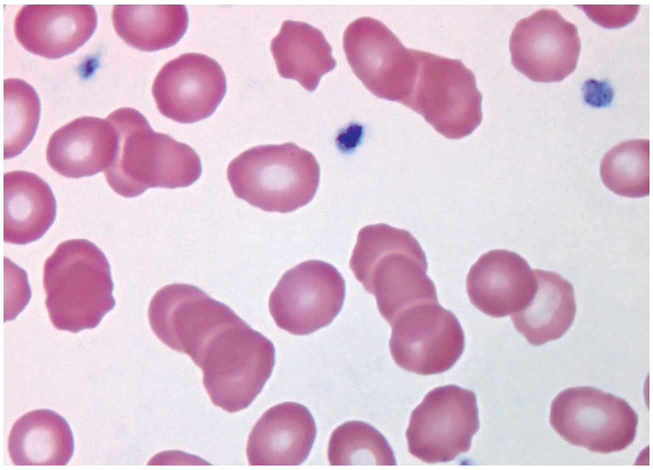

Figure 39.16. *Rouleaux. Stacking of red blood cells in a linear pattern distinguishes rouleaux from agglutination (Figure 39.10). Rouleaux are most commonly associated with hypergammaglobulinemia, especially in HIV infection or monoclonal plasma cell disorders (peripheral blood smear; Wright-Giemsa).*

(Courtesy of Curtis A. Hanson, MD, Mayo Clinic, Rochester, Minnesota; used with permission.)

be identified) and to discontinue the use of drugs that have been implicated in hemolysis.

Paroxysmal Cold Hemoglobinuria (Complement-Mediated Lysis)

Paroxysmal cold hemoglobinuria is the least common cause of autoimmune hemolytic anemias. A positive Donath-Landsteiner test is diagnostic; it detects an IgG antibody that binds to RBCs at low temperatures, which causes hemolysis. Paroxysmal cold hemoglobinuria is often idiopathic and can be associated with syphilis, mononucleosis, mycoplasma, and childhood exanthems. The condition usually resolves after the infection clears.

KEY FACTS

- ✓ Acute chest syndrome—
    - leading cause of death in sickle cell anemia
    - clinical features: fever, chest pain, tachypnea, leukocytosis, and pulmonary infiltrates
- ✓ Sickle cell anemia therapy—immunizations for encapsulated organisms, penicillin prophylaxis, and folate supplementation
- ✓ Increased RBC destruction in hemolytic anemia—increased indirect bilirubin and lactate dehydrogenase levels; decreased haptoglobin level
- ✓ Hemosiderinuria—evidence that desquamated renal tubular cells absorbed free hemoglobin days to weeks earlier
- ✓ Cold agglutinin syndrome—idiopathic (usually) or secondary to infection (*Mycoplasma pneumonia* or EBV) or malignant process

DAT-Negative Hemolytic Anemia

The differential diagnosis of DAT-negative hemolytic anemia is broad and includes hereditary RBC disorders such as enzymopathies (eg, G6PD deficiency and pyruvate kinase deficiency), hemoglobinopathies, and membrane disorders; paroxysmal nocturnal hemoglobinuria; Wilson disease; and microangiopathic conditions, including thrombotic thrombocytopenic purpura (TTP). Rarely, warm agglutinin autoimmune hemolytic anemia is DAT-negative owing to low antibody titers.

G6PD Deficiency

G6PD deficiency, a sex-linked disorder, is the most common RBC enzyme deficiency. It causes decreased levels of glutathione (an antioxidant), which makes RBCs more sensitive to oxidative damage by infections, toxins (eg, naphthalene in mothballs), and drugs. G6PD deficiency confers some protection against falciparum malaria.

Hemolysis does not usually occur in the steady state but occurs with infections, diabetic ketoacidosis, ingestion of fava beans (seen only in G6PD Mediterranean), and drugs. Drugs that commonly cause hemolysis include antimalarial agents (eg, primaquine and chloroquine), dapsone, sulfonamides, nitrofurantoin, high-dose aspirin, probenecid, and nitrites.

Abnormal laboratory findings include intravascular hemolysis, methemoglobinemia, and methemalbuminemia (specific for intravascular hemolysis due to enzymopathy). Supravital staining for Heinz bodies is a good screening test, but their absence does not rule out the diagnosis. The G6PD assay is the definitive test but should not be done during acute hemolysis. Therapy includes treating the underlying infection and withdrawing use of the offending drug.

Hereditary Spherocytosis

Hereditary spherocytosis is typically an autosomal dominant disorder, but it can be autosomal recessive or sporadic. It is caused by an underlying defect in the RBC cytoskeleton because of a partial gene deficiency (eg, in ankyrin or spectrin). Features include jaundice, splenomegaly, negative DAT, spherocytes, and increased osmotic fragility. The osmotic fragility test is almost always abnormal and is the most reliable diagnostic test. Pigment gallstones are present in most patients by age 50 years. Treatment is splenectomy after the first decade of life for moderate or severe hemolysis, which invariably reduces hemolysis. Asymptomatic adults may be observed if the hemoglobin concentration is greater than 11 g/dL and the reticulocyte count is less than 6%.

Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired, clonal, stem cell disorder. Blood cells are unusually sensitive to activated complement and are lysed primarily at night when plasma is more acidotic from sleep-related physiology (eg, relative hypoxia).

A mutation in the *PIGA* gene causes cells in PNH to have a decrease or absence of glycosylphosphatidylinositol (GPI)-linked proteins, including CD14, CD55, and CD59. Clinically, PNH is characterized by chronic intravascular hemolytic anemia, pancytopenia, and venous thrombosis of the portal system, brain, and extremities. Budd-Chiari syndrome (hepatic vein thrombosis) is the main cause of death. In up to 10% of patients, myelodysplasia or acute myeloid leukemia develops. The most useful assay for diagnosis of PNH is flow cytometry to establish the absence of the GPI-linked antigens. Up to 60% of patients respond to prednisone; eculizumab is a complement (C5) monoclonal antibody that can be used for long-term therapy for hemolysis in PNH.

Thrombotic Microangiopathies

Differential Diagnosis

In microangiopathic hemolytic anemia, RBCs are fragmented and deformed by fibrin deposits in the peripheral blood (Figure 39.17). DAT results are negative. The associated disorders, characterized by widespread microvascular thrombosis leading to end-organ injury, include TTP, hemolytic uremic syndrome (HUS), malignant hypertension, pulmonary hypertension, acute glomerulonephritis, renal allograft rejection, obstetric catastrophes, HELLP syndrome (hemolysis, elevated liver function tests, and low platelet count), disseminated intravascular coagulopathy, collagen vascular diseases (scleroderma), vascular malformations including Kasabach-Merritt syndrome (giant hemangiomas that trap platelets), viral infections (HIV), bacterial infections (*E coli* O157:H7), drug-induced disorders (eg, mitomycin C, quinine, ticlopidine, tacrolimus, cisplatin, and cyclosporine), bone marrow transplant, and solid organ transplant.

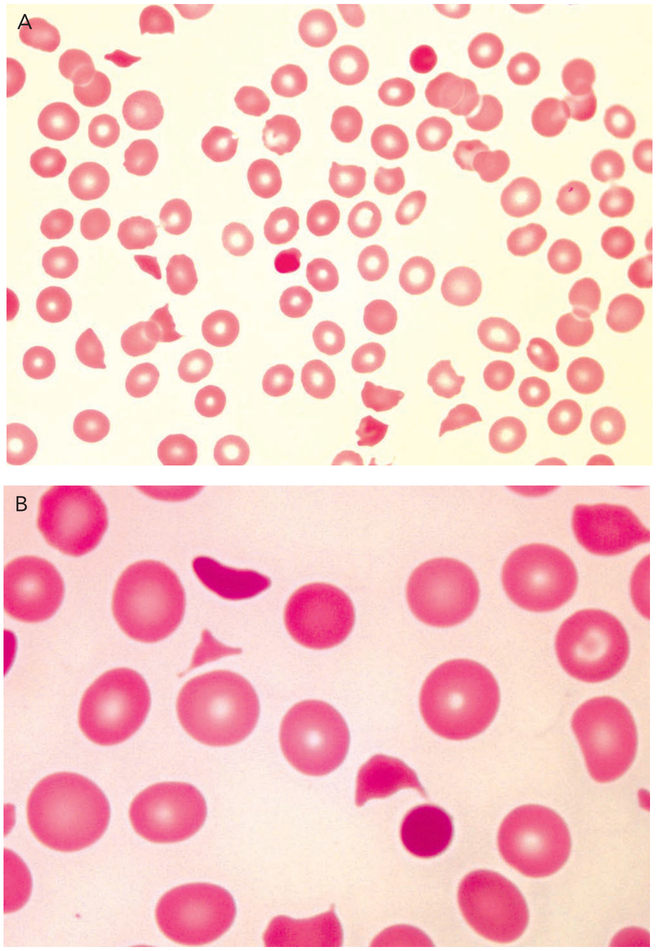

Figure 39.17. *Schistocytes. Fragmented red blood cells are shaped like helmets, triangles, or kites. These are characteristic of any microangiopathic hemolytic process (peripheral blood smear; Wright-Giemsa).*

(Courtesy of Curtis A. Hanson, MD, Mayo Clinic, Rochester, Minnesota; used with permission.)

Thrombotic Thrombocytopenic Purpura

The features of TTP include the pentad of microangiopathic hemolytic anemia, thrombocytopenia, neurologic signs (headache, coma, mental changes, paresis, seizure, aphasia, syncope, visual symptoms, dysarthria, vertigo, agitation, confusion, and delirium), fever, and kidney abnormalities (abnormal urinary sediment and increased creatinine level). Most patients do not have all 5 features. The primary criteria are thrombocytopenia and microangiopathy, and these are sufficient to establish the diagnosis. The anemia is normochromic normocytic, with microangiopathic hemolytic features (Figure 39.17). DAT results are negative. Results of coagulation studies are normal, in contrast to abnormal results in disseminated intravascular coagulopathy. The cause of TTP is unknown in more than 90% of patients; however, it is associated with pregnancy, use of oral contraceptives, HIV infection, cancer, bone marrow transplant, certain chemotherapy drugs (especially mitomycin C, bleomycin, and gemcitabine), and other drugs (eg, crack cocaine, ticlopidine, and cyclosporine).

Patients with TTP are deficient in the von Willebrand factor–cleaving protease ADAMTS13. Even when ADAMTS13 assays are available, results can take days to return; thus, the assay is not useful for initial treatment decisions.

Without treatment, more than 90% of patients die of multiorgan failure, but with treatment, 70% to 80% survive the disease and have few or no sequelae. The treatment of choice is plasma exchange. Relapses are also managed with plasma exchange. The management of refractory TTP includes high-dose glucocorticoids, rituximab, cyclophosphamide, and splenectomy. Platelet transfusion should be avoided because it can exacerbate the disease.

Hemolytic Uremic Syndrome

HUS is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Fever and neurologic signs are usually not present. It is associated with infections (*E coli* O157:H7 and *Shigella dysenteriae*), pregnancy, bone marrow transplant, chemotherapy, and immunosuppressive medications such as cyclosporine. HUS is usually not associated with a decrease in ADAMTS13 activity. Management of HUS is supportive. In adults, treatment with plasma exchange is indicated, but the response is variable.

KEY FACTS

- ✓ G6PD deficiency—drugs that cause hemolysis include antimalarial agents, dapsone, sulfonamides, nitrofurantoin, high-dose aspirin, probenecid, and nitrites
- ✓ Hereditary spherocytosis—abnormal osmotic fragility test
- ✓ PNH—activated complement lyses sensitive blood cells primarily during sleep (more acidotic)
- ✓ TTP pentad of features—
  - microangiopathic hemolytic anemia
  - thrombocytopenia
  - neurologic signs
  - fever
  - kidney abnormalities

Transfusion Reactions

Causes

The primary cause of major transfusion reactions and transfusion-related deaths is medical error, which includes bypassed safeguards, similar patient names, and verbal or faxed communications. The major transfusion reactions include acute hemolytic transfusion reactions, transfusions associated with anti-IgA antibodies, transfusion-related acute lung injury (TRALI), acute respiratory distress syndrome (ARDS), delayed hemolytic transfusion reactions, febrile transfusion reactions, urticarial (allergic) transfusion reactions, and circulatory overload (Table 39.3).

Acute Hemolytic Transfusion Reactions

Acute hemolytic transfusion reactions are the most life-threatening transfusion reactions and occur within minutes to hours. The recipient's RBC antibodies (usually IgM) react against the donor's RBCs and cause complement-mediated hemolysis. The most common cause is human error, especially when blood is released emergently. The mortality rate is about 20%; of the fatal transfusion reactions, 85% involve ABO incompatibility (Table 39.4). Other, nonclerical causes include antibodies not detected before transfusion, such as Kell, Duffy (Fy^a), and Kidd (Jk^a). Clinically, patients have pain at the intravenous site, a sense of impending doom, back pain, abdominal pain, fever, chills, chest pain, hypotension, nausea, flushing, and dyspnea. The DAT is positive in most cases.

Table 39.3 • Risks of Complications From Transfusions in the United States

Complication	Risk Per Units of Transfused Blood
Minor allergic reaction	3/100
Circulatory overload	Variable
Febrile, nonhemolytic	3/100
Delayed hemolytic transfusion reaction	1/4,000
TRALI	1/10,000
Acute hemolytic transfusion reaction	$1/2.5\times10^4$ to $1/1.0\times10^6$
HIV infection	$1/2.1\times10^6$
Hepatitis B virus infection	$1/2.0\times10^5$
Hepatitis C virus infection	$1/1.9\times10^5$
HTLV type I or II infection	$1/2.0\times10^5$
West Nile virus infection	Unknown
Bacterial infections	1/2,000 to $1/5.0\times10^5$
IgA-related anaphylaxis	$1/1.0\times10^5$
Graft-vs-host disease	Rare
Immunosuppression	Unknown
Posttransfusion purpura	Rare
Prion infection	Unknown

Abbreviations: HIV, human immunodeficiency virus; HTLV, human T-cell leukemia virus; Ig, immunoglobulin; TRALI, transfusion-related acute lung injury.

Complications include oliguria, acute kidney injury, and disseminated intravascular coagulation. Treatment includes immediate termination of the transfusion, vigorous administration of fluids, and furosemide to increase renal cortical blood flow.

Allergic Transfusion Reactions

Allergic transfusion reactions are a complication in 3% of transfusions and are caused by a recipient's antibody against foreign-donor serum proteins. Transfusion reactions can also be associated with anti-IgA antibodies. These include anaphylactic reactions, which occur most commonly in patients with IgA deficiency who may have circulating complement-binding

Table 39.4 • Blood Product Compatibility in the ABO System[a]

	Acceptable Donor ABO Groups		
Recipient ABO Group	Packed Red Blood Cells	Platelets and Fresh Frozen Plasma	Whole Blood (Rarely Used)
O	O	AB, A, B, or O	O
A	A or O	A or AB	A
B	B or O	B or AB	B
AB	AB, A, B, or O	AB	AB

[a] Natural alloimmunization against A and B antigens occurs in people lacking these antigens. Upon transfusion of ABO-incompatible blood, preformed antibodies serve as hemagglutinins, resulting in life-threatening acute hemolysis and complement activation. Hemagglutinins are found primarily in plasma; platelets are considered similar to plasma products with respect to ABO compatibility.

anti-IgA antibodies that react with donor IgA. Clinical features are similar to those of an acute hemolytic transfusion reaction. Treatment includes stopping the transfusion and giving antihistamines and conventional antianaphylactic drugs. Transfusion protocols for patients include use of washed RBCs and IgA-deficient plasma.

Transfusion-Related Acute Lung Injury

Transfusion-associated ARDS or TRALI results from an interaction between the recipient's leukocytes and donor antileukocyte antibodies. TRALI often is unrecognized and ranks third among causes of transfusion-related deaths. It is characterized by acute respiratory distress during transfusion or within 6 hours after completion of transfusion, hypotension, bilateral pulmonary infiltrates, normal or low pulmonary capillary wedge pressure, no evidence of circulatory overload, and fever. With appropriate supportive care, recovery is rapid, occurring in 24 to 48 hours.

Delayed Hemolytic Transfusion Reactions

Delayed hemolytic transfusion reactions (occurring in 1 in 4,000 transfusions) occur because of the inability to detect clinically significant recipient antibodies before transfusion. The reaction usually occurs 5 to 10 days after transfusion and is less dangerous than an acute hemolytic reaction. The recipient's plasma contains antibody before transfusion because of a previous transfusion or previous pregnancy. There is evidence of hemolysis, and DAT results are positive. One-third of the patients are asymptomatic, and the reactions are detected by the recurrence of laboratory-detected anemia without clear cause; other patients have symptoms of anemia, chills, jaundice, and fever. Management consists of monitoring hemoglobin concentration and renal output and avoiding the use of units with the offending antigen in the future.

Febrile Transfusion Reactions

Febrile transfusion reactions are characterized by chills, fever, flushing, headache, tachycardia, myalgias, and arthralgias. They usually begin about 1 hour after the transfusion starts and last for 8 to 10 hours. They occur in 1% of all transfusions. Causes include cytokines from leukocytes and platelets against donor antigens and antiserum protein antibodies. Treatment consists of stopping the transfusion to evaluate the patient; initially, a febrile reaction cannot be distinguished from a hemolytic transfusion reaction. Preventive methods include leukoreduction.

Circulatory Overload

Circulatory overload may cause tightness in the chest, dry cough, and acute edema. It occurs in patients who already have an increased intravascular volume or decreased cardiac reserve, with symptoms generally developing within several hours after transfusion. Management includes slowing the transfusion to 100 mL/h, placing the patient in the sitting position, and giving diuretics.

Posttransfusion Purpura

Posttransfusion purpura is a rare syndrome in which the recipient makes antiplatelet antibodies, which cause an abrupt onset of severe thrombocytopenia 5 to 10 days after blood transfusion. Most cases involve patients who lack human platelet antigen 1a and who have an antibody from a previous pregnancy or transfusion.

Infection

Pathogen transmission may occur with transfusions. These risks and other risks of transfusion are summarized in Table 39.3.

Porphyria

The porphyrias are enzyme disorders that are autosomal dominant with low disease penetrance, except for congenital erythropoietic porphyria (which is autosomal recessive) and porphyria cutanea tarda (which may be acquired and is associated with hepatitis C and hemochromatosis). Most persons remain biochemically and clinically normal throughout most of their lives. Clinical expression is linked to environmental and acquired factors.

Disease manifestations depend on the type of excess porphyrin intermediate. If the earlier precursor molecules (δ-aminolevulinic acid and porphobilinogen) are in excess, the clinical manifestations are neuropsychiatric, including autonomic dysfunction (abdominal pain, vomiting, constipation, tachycardia, and hypertension), psychiatric symptoms, fever, leukocytosis, and paresthesias. If the excess is in the later intermediates (uroporphyrins, coproporphyrins, and protoporphyrins), the manifestations are cutaneous (photosensitivity, blister formation, facial hypertrichosis, and hyperpigmentation). An

Table 39.5 • Comparison of Porphyrias

Porphyria Cutanea Tarda	Acute Intermittent Porphyria	Porphyria Variegata
Features		
Most common type of porphyria Iron overload Skin lesions on light-exposed areas Hypertrichosis (usually mild) Increased uroporphyrins in urine No neuropathic features	Increased urinary δ-aminolevulinic acid and porphobilinogen levels during acute symptomatic episodes, with normal levels between episodes Neurologic symptoms: abdominal pain of 3-5 days' duration without anatomical cause, focal neurologic problems such as polyneuropathy and motor paresis, psychiatric problems with hallucinations, confusion, psychosis, seizures Decreased porphobilinogen deaminase activity Normal protoporphyrin and coproporphyrin levels in stool	Clinically: photosensitivity, abdominal pain, neurologic symptoms similar to those in acute intermittent porphyria Increased protoporphyrin and coproporphyrin levels in stool
Associations		
Alcoholic liver disease, chronic hepatitis C, hemochromatosis Estrogens: females; males treated for prostatic carcinoma Hexachlorobenzene exposure	Drugs can precipitate crises (eg, sulfonamides, barbiturates, alcohol) Menstrual cycle can exacerbate symptoms Infection or surgery can precipitate crisis Inadequate nutrition can precipitate crisis	Common in South Africa (due to founder effect), Netherlands
Treatment		
Phlebotomy to remove iron Chloroquine Low-dose antimalarials	Avoid prolonged fasting and crash diets Large amounts of carbohydrate (400 g daily) Intravenous hematin Luteinizing hormone–releasing hormone agonists for suppression of hormonal fluctuation	Same as for acute intermittent porphyria

excess of both early and late porphyrins results in both neuropsychiatric and cutaneous manifestations.

Porphobilinogen production and excretion are increased during marked symptoms caused by the 3 neuropathic porphyrias, which include acute intermittent porphyria, hereditary coproporphyria, and porphyria variegata. Hereditary coproporphyria and porphyria variegata are characterized by an accumulation of coproporphyrinogen/coproporphyrin or protoporphyrinogen/protoporphyrin and a concomitant increase in δ-aminolevulinic acid and porphobilinogen. The 24-hour urinary porphobilinogen level should be determined during an episode of acute porphyria. Patients with acute intermittent porphyria lack skin lesions. It is important to check fecal porphyrins in protoporphyria, porphyria variegata, and coproporphyria. An increased coproporphyrin level alone, therefore, does not support a diagnosis of porphyria. The porphyrias are compared in Table 39.5.

KEY FACTS

✓ Acute hemolytic transfusion reactions—usually from human error, especially with emergent release of blood

✓ TRALI—acute respiratory distress during transfusion or ≤6 hours after transfusion

✓ TRALI—hypotension, bilateral pulmonary infiltrates, normal or low pulmonary capillary wedge pressure, no evidence of circulatory overload, and fever

✓ Acute porphyrias—24-hour urinary porphobilinogen level should be measured during an occurrence

40

Bleeding Disorders[a]

RAJIV K. PRUTHI, MBBS

Functions of the Coagulation System

The 2 essential functions of the coagulation system (maintaining hemostasis and preventing and limiting thrombosis) are served by the procoagulant and anticoagulant components. Vascular injury results in activation of the phases of hemostasis, including vasospasm, platelet plug formation (platelet activation, adhesion, and aggregation), and fibrin clot formation (by activation of coagulation factors in the procoagulant system). The anticoagulant system controls excessive clot formation, whereas the fibrinolytic system breaks down and remodels blood clots.

Evaluation for a Bleeding Disorder

Bleeding disorders consist of clotting factor deficiencies or inhibitors, vascular bleeding disorders, and platelet disorders (quantitative and qualitative). Each of these is broadly classified into congenital disorders and acquired disorders.

The best screening tool to evaluate for a bleeding disorder is a thorough clinical evaluation (personal and family bleeding history and physical examination). The presence of a bleeding disorder may be suggested from inquiry into the presence and age at onset of spontaneous bleeding (eg, epistaxis, easy bruising, or joint bleeding), unusual or unexpected posttraumatic or surgical bleeding (including from dental extractions), and family history. A thorough clinical evaluation should also include review of medications and coexisting medical problems to identify clinical risk factors for bleeding.

Laboratory Testing to Evaluate a Patient With Abnormal Bleeding

Tests to evaluate a patient with abnormal bleeding should include a complete blood cell count (CBC), prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen levels. Additional testing that may not be generally available includes assays for von Willebrand disease (vWD); other coagulation factor assays may be indicated depending on the results of initial screening tests. If no diagnosis is made, factor XIII (FXIII) assays and platelet function tests may be indicated.

Prothrombin Time (International Normalized Ratio)

The PT assesses the extrinsic and final common pathways of the procoagulant cascade (Figure 40.1). Prolonged PT is caused by deficiencies or inhibitors of clotting factors. The PT is mainly useful as a monitoring test for warfarin anticoagulation and as an initial screening test for patients who have bleeding symptoms. The international normalized ratio reduces interlaboratory variation of the PT and is calculated and reported by the laboratory; its main role is in monitoring warfarin anticoagulation. Preoperative patients do not need routine PT testing.

Activated Partial Thromboplastin Time

The aPTT assesses the intrinsic and final common pathways of the procoagulant cascade (Figure 40.1); deficiencies or inhibitors of clotting factors within the intrinsic and final common pathways result in prolongation of the aPTT. The aPTT is commonly used to monitor unfractionated heparin (UFH) therapy

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[a] Portions previously published in Pruthi RK. A practical approach to genetic testing for von Willebrand disease. Mayo Clin Proc. 2006 May;81(5):679-91; and Kamal AH, Tefferi A, Pruthi RK. How to interpret and pursue an abnormal prothrombin time, activated partial thromboplastin time, and bleeding time in adults. Mayo Clin Proc. 2007 Jul;82(7):864-73; used with permission of Mayo Foundation for Medical Education and Research.

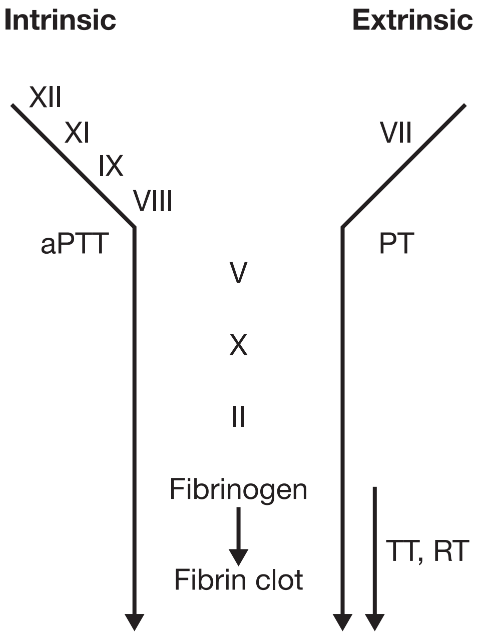

Figure 40.1. *Coagulation Cascade. Factors in the intrinsic, extrinsic, and final common pathway are shown, along with points in the pathways addressed by various tests. aPTT indicates activated partial thromboplastin time; PT, prothrombin time; RT, reptilase time; TT, thrombin time.*

and direct thrombin inhibitor therapy (eg, argatroban) and as an initial screening test for the presence of lupus anticoagulant or for patients who have bleeding symptoms.

Approach to a Prolonged PT or aPTT

If a patient has a prolonged PT, aPTT, or both, artifactual causes (eg, increased hematocrit; nonfasting, lipemic sample; or heparin contamination of the specimen) should first be excluded. Second, a mixing study should be performed in a 1:1 ratio with normal pooled plasma. If the clotting time (PT or aPTT) normalizes, a coagulation factor deficiency is implied, and follow-up factor assays are then performed. If the PT or aPTT is inhibited (ie, shortens but does not normalize), it implies that an inhibitor is present. The inhibitors may be medications (eg, heparins and direct thrombin inhibitors), specific factor inhibitors (eg, factor VIII [FVIII] or factor V inhibitors), or nonspecific inhibitors (eg, lupus anticoagulants). Appropriate follow-up testing typically leads to the diagnosis of the underlying cause of the prolonged PT and aPTT.

Bleeding Disorders Not Detected With PT and aPTT

Several bleeding disorders are not detected with the PT and aPTT (Box 40.1).

Box 40.1 • Disorders Not Detected With the PT and aPTT

- Qualitative platelet defects (requires specialized platelet function testing)
- von Willebrand disease (requires assays for von Willebrand factor)
- Factor XIII deficiency (requires specialized factor XIII screening or functional assays)
- Deficiency of antiplasmin and plasminogen activator inhibitor 1 (requires specific assays)

Abbreviations: aPTT, activated partial thromboplastin time; PT, prothrombin time.

KEY FACTS

- ✓ Essential functions of coagulation system—maintaining hemostasis (procoagulant component) and limiting thrombosis (anticoagulant component)
- ✓ Screening for a bleeding disorder—thorough clinical evaluation is the best tool
- ✓ PT—assesses extrinsic and final common pathways of the procoagulant cascade
- ✓ aPTT—assesses intrinsic and final common pathways of the procoagulant cascade

Congenital Plasmatic Bleeding Disorders (Factor Deficiencies)

Of the congenital plasmatic bleeding disorders, vWD is the most common. Others include hemophilia A, hemophilia B, and hemophilia C. Other factor deficiency states are rare (Table 40.1). All clotting factors are produced by the liver except von Willebrand factor (vWF), which is produced by vascular endothelial cells and megakaryocytes.

von Willebrand Disease

Definition and Classification

vWD is a deficiency or dysfunction of vWF. It is classified according to whether the defect is quantitative (types 1 and 3) or qualitative (types 2A, 2B, 2M, and 2N).

Key Definition

von Willebrand disease: *deficiency or dysfunction of vWF.*

Table 40.1 • Congenital Bleeding Disorders

Congenital Disorder	Deficient Factor	PT	aPTT	Prevalence	Mode of Inheritance
Hemophilia A	Factor VIII	NL	Prol	1:5,000[a]	X-linked recessive
Hemophilia B	Factor IX	NL	Prol	1:30,000[a]	X-linked recessive
Hemophilia C	Factor XI	NL	Prol	Up to 4%[b]	Autosomal recessive
von Willebrand disease	von Willebrand factor	NL	NL or Prol	Up to 1%	Autosomal dominant or recessive
Factor VII deficiency	Factor VII	Prol	NL	1:500,000	Autosomal recessive
Rare coagulation factor deficiencies					
Factor V	Factor V	Prol	Prol	1:1 million	Autosomal recessive
Factor II	Factor II	Prol	NL or Prol	Rare	Autosomal recessive
Factor X	Factor X	Prol	NL or Prol	1:500,000	Autosomal recessive
Factor XIII	Factor XIII	NL	NL	Rare	Autosomal recessive
Combined factors VIII and V	Factors VIII and V	Prol	Prol	Rare	Autosomal recessive

Abbreviations: aPTT, activated partial thromboplastin time; NL, normal; Prol, prolonged; PT, prothrombin time.

[a] Live male births.

[b] Among Ashkenazi Jews.

Biochemistry and Function of vWF

Endothelial cells and platelets store vWF. After it is secreted, the most hemostatically active ultra-large-molecular-weight multimers of vWF are cleaved into multimers of smaller size by a protease, ADAMTS13. vWF mediates platelet adhesion and aggregation. It acts as a carrier protein for FVIII, protecting it from proteolytic inactivation.

Clinical Features

Patients who have mild vWD may be asymptomatic and have bleeding only when challenged with trauma or minor surgery (eg, dental extraction) or major surgery.

Patients who have severe vWD may have spontaneous bleeding. Spontaneous bleeding is typically mucocutaneous (bruising, epistaxis, hematuria, or gastrointestinal tract hemorrhage); in type III vWD, bleeding occurs in joints and soft tissue. Bleeding may be exacerbated by the use of aspirin or nonsteroidal analgesics.

Laboratory Testing

Laboratory evaluation includes testing for vWF antigen, vWF activity (also known as ristocetin cofactor activity), and FVIII activity (Box 40.2). If initial results are abnormal, vWF multimer analyses are performed to determine the subtype of vWD (Box 40.3).

Variables Affecting vWF Levels

Healthy people with blood group O have vWF levels that are 25% to 30% lower than in people with blood groups A, B, or AB and thus may receive a misdiagnosis of vWD. Therefore, ABO typing should be part of the initial testing.

Acquired defects of vWF (ie, *acquired von Willebrand syndrome*) may occur in patients with anatomical cardiac abnormalities (eg, aortic stenosis, hypertrophic cardiomyopathy, or placement of left ventricular assist devices), myeloproliferative disorders, or monoclonal protein disorders. The syndrome mimics congenital type 2 vWD.

Short-term physical exertion, inflammation, malignant processes, hyperthyroidism, estrogens, and pregnancy increase vWF levels to normal and may mask a diagnosis of vWD. Hypothyroidism is associated with decreased vWF levels.

Type 2B vWD is associated with thrombocytopenia. Type 2N vWD results from mutations in the FVIII binding domain of vWF. This subtype may be mistaken for mild hemophilia A.

Box 40.2 • Stepwise Approach to Assessment for von Willebrand Disease (vWD)

1. Bleeding history
2. Complete blood cell count
3. vWD profile testing
   - vWF:Ag
   - RCoF
   - VIII:c
4. ABO blood group
5. Optional tests if initial data suggest vWD
   - vWF multimers
   - vWF:CBA
   - vWF:VIIIB
   - RIPA
6. Genetic tests if indicated

Abbreviations: Ag, antigen; CBA, collagen-binding assay; VIIIB, factor VIII binding assay; VIII:c, factor VIII coagulant activity; RCoF, ristocetin cofactor; RIPA, ristocetin-induced platelet aggregation; vWF, von Willebrand factor.

Box 40.3 • Subtypes of von Willebrand Disease

Type 1—mild to moderate decrease in the level and activity of vWF:Ag

Type 2—disproportionate decrease in the activity of functional vWF, called the *ristocetin cofactor* (RCoF), compared with vWF:Ag

Type 3—absence of vWF

Abbreviations: vWF, von Willebrand factor; vWF:Ag, von Willebrand factor antigen.

Inheritance of vWD

Type 1 vWD is inherited as an autosomal dominant trait with variable penetrance. Types 2A, 2B, and 2M vWD are inherited as autosomal dominant traits. Type 3 vWD and type 2N (Normandy) vWD are inherited as autosomal recessive traits.

Management

The goals for managing vWD include preventing and treating hemorrhage (Box 40.4). If a diagnosis of vWD has been established, a treatment trial of desmopressin acetate should be performed for patients with types 1, 2A, or 2M vWD. Intravenous infusion of 0.3 mcg/kg body weight releases vWF from its storage sites; levels should be measured 60 minutes and 4 hours after infusion. Desmopressin is generally not helpful if patients have type 2B vWD because the release of endogenous vWF worsens thrombocytopenia. Patients with type 3 vWD have no response to desmopressin and should not undergo a desmopressin trial. Desmopressin is indicated for prevention or treatment of minor bleeding, for minor procedures such as dental extraction, and for the management of menorrhagia in women with vWD. An intranasal formulation of desmopressin is also available, but the concentration and dose are higher than those used for nocturnal enuresis. For patients who have no response to desmopressin and for those in whom it is contraindicated or not useful (eg, type 3 vWD), administration of purified plasma-derived vWF or recombinant vWF concentrates is the therapy of choice.

Box 40.4 • Management of von Willebrand Disease

- General measures
  - Provide patient education
  - Recommend a medical condition identification tag
  - Generate treatment guidelines for managing bleeding
  - Refer to a comprehensive hemophilia treatment center for periodic follow-up
- Specific measures
  - Administer desmopressin
  - Administer adjunctive ε-aminocaproic acid or vWF concentrates preoperatively to prevent bleeding or to manage bleeding
  - Administer vWF concentrates

Abbreviation: vWF, von Willebrand factor.

Hemophilia A and Hemophilia B

Hemophilia A and hemophilia B are clinically indistinguishable, X-linked recessive bleeding disorders. Hemophilia A is due to a deficiency in blood coagulation FVIII, and hemophilia B is due to a deficiency in factor IX (FIX). Hemophilia is classified according to the level of FVIII or FIX as severe (<1%), moderate (1%-5%), or mild (6%-40%).

Clinical Features

Patients who have *mild hemophilia* seldom experience spontaneous hemorrhage but will have bleeding after trauma or surgery; rarely, they may not receive a diagnosis of hemophilia until adulthood. Patients who have *moderate hemophilia* experience spontaneous bleeding infrequently but typically have bleeding after minor trauma and surgery.

Patients who have *severe hemophilia* frequently experience spontaneous bleeding, including hemarthrosis, soft tissue hematomas, and intracranial hemorrhage, in addition to minor hemorrhage such as epistaxis and ecchymoses. Regular prophylactic administration of FVIII concentrates to patients with severe disease has decreased the frequency of and associated chronic complications related to bleeding.

Management

At the initial diagnosis of mild or moderate hemophilia A, as with vWD, a desmopressin treatment trial is started; FVIII levels are checked before infusion and 1 hour after infusion. For patients who have hemophilia A and respond to desmopressin, it is administered for *minor* hemorrhage or for prophylaxis and treatment of minor surgical hemorrhage. Recombinant or plasma-derived FVIII concentrates are used as therapy for *major* hemorrhages and as prophylaxis for major surgery.

Desmopressin is not used for hemophilia B; instead, recombinant or plasma-derived FIX concentrates are used.

Complications of Treatment

Transfusion-transmitted viral infections can occur (eg, viral hepatitis and HIV infection), although with contemporary clotting factor manufacturing processes and the introduction of recombinant factors, these are rare. *Recurrent hemarthrosis* (in severe hemophilia and in patients who have

FVIII or FIX inhibitors) leads to premature degenerative joint disease. *Development of FVIII and FIX inhibitors* is the most serious complication. Standard FVIII and FIX concentrates are ineffective for prevention and treatment of bleeding, and bypassing agents (eg, recombinant factor VIIa or activated prothrombin complex concentrates) are required.

Factor VII Deficiency

Factor VII deficiency is typically a mild bleeding disorder that is usually detected with a preoperative prolonged PT. Factor VII levels as low as 10% of the reference value may be undetected for many years because patients do not typically have bleeding symptoms. Bleeding symptoms are similar to those of hemophilia. Recombinant factor VIIa is the therapy of choice for preventing and treating hemorrhage; however, fresh frozen plasma is also an option.

Factor XI Deficiency (Hemophilia C)

Factor XI (FXI) deficiency is a rare autosomal recessive disorder that is prevalent among Ashkenazi Jews. It is a mild bleeding disorder; patients usually have bleeding after surgery or trauma or after starting therapy with antiplatelet agents or anticoagulants.

Bleeding symptoms do not correlate well with FXI levels (ie, patients with mild deficiencies may have substantial bleeding symptoms, whereas patients with more severe deficiencies may remain asymptomatic until after surgery or initiation of an anticoagulant or antiplatelet agent).

Fresh frozen plasma is the most widely available choice for prevention and treatment of hemorrhage. FXI concentrates are being studied in clinical trials.

FXIII Deficiency

FXIII deficiency has an autosomal recessive inheritance pattern. Severe FXIII deficiency is characterized by clinically significant bleeding but normal results of screening tests (PT and aPTT). Other characteristics include umbilical cord bleeding, delayed wound healing, delayed hemorrhage, and recurrent pregnancy loss. Cryoprecipitate and FXIII concentrates are the primary choice for prevention and treatment of hemorrhage.

Factor Deficiencies That Prolong the aPTT But Do Not Result in Hemorrhage

Deficiencies of factor XII, high-molecular-weight kininogen, and prekallikrein can result in a marked prolongation of the aPTT, yet even severe deficiencies are not risk factors for hemorrhage. Their roles in hemostasis are being defined.

KEY FACTS

- ✓ Mild vWD—patients may be asymptomatic and have bleeding only with trauma or surgery
- ✓ Severe vWD—patients may have spontaneous bleeding (typically bruising, epistaxis, hematuria, or gastrointestinal tract hemorrhage)
- ✓ Hemophilia A and hemophilia B—
  - clinically indistinguishable
  - X-linked recessive bleeding disorders
- ✓ Factor VII deficiency—
  - typically mild bleeding disorder
  - usually detected with a preoperative prolonged PT
- ✓ FXI deficiency—
  - rare autosomal recessive mild bleeding disorder
  - prevalent among Ashkenazi Jews
- ✓ FXIII deficiency—
  - autosomal recessive inheritance
  - if severe, characterized by clinically significant bleeding but normal PT and aPTT results

Acquired Bleeding Disorders

Acquired bleeding disorders can result from decreased production of coagulation factors by the liver (as in liver disease), increased consumption of coagulation factors (as in disseminated intravascular coagulation [DIC] and fibrinolysis), or the development of inhibitors against coagulation factors (Table 40.2).

Liver Disease

Because most procoagulant and anticoagulant factors (except vWF) are produced in the liver, hepatocellular damage and liver failure lead to decreased production of both classes of proteins. In general, there is a balance between bleeding and thrombosis, but triggering factors such as infections may tip the balance to either bleeding or thrombosis. Coagulation assays such as PT and aPTT are prolonged, so there is a mistaken belief that these patients have a bleeding tendency when, in fact, they may be at risk for thrombosis (eg, portal vein thrombosis). Empiric transfusion of fresh frozen plasma or cryoprecipitate simply to correct laboratory abnormalities is discouraged. When indicated, supportive management includes replenishment of the

Table 40.2 • Causes of Acquired Coagulation Factor Deficiencies

Cause of Deficiency	Deficient Factor
Warfarin	Vitamin K–dependent factors
Decreased nutritional intake or malabsorption	Vitamin K–dependent factors
Liver failure	Multiple factors
Amyloid	Factor X
Myeloproliferative disease	Factor V
Acquired von Willebrand syndrome	von Willebrand factor and factor VIII
Disseminated intravascular coagulation	Multiple factors

deficient coagulation factors with fresh frozen plasma (cryoprecipitate is a more concentrated form for fibrinogen and FXIII) until the liver recovers or is replaced by a transplanted liver.

Disseminated Intravascular Coagulation

DIC is a dynamic process with various causes that result in microvascular thrombosis and consumption of clotting factors (Box 40.5).

Box 40.5 • Causes of DIC

- Acute and subacute DIC
    - Cancers (hematologic or solid organ)
    - Infection or sepsis (bacterial)
    - Obstetric complications (placental abruption or amniotic fluid embolism)
    - Massive trauma
    - Burns
    - Advanced liver disease
    - Snake bite
    - Hemolytic transfusion reaction
- Chronic DIC
    - Solid tumors
    - Obstetric complications (retained dead fetus)
    - Advanced liver disease
- Localized causes of systemic DIC
    - Aortic aneurysm
    - Giant hemangiomas

Abbreviation: DIC, disseminated intravascular coagulation.

Clinical Features

DIC should be suspected in patients with underlying conditions known to predispose to DIC (Box 40.5). At initial evaluation, most patients have new-onset bleeding; occasionally, patients have thrombosis or both bleeding and thrombosis.

Bleeding manifestations include bleeding from surgical wounds and venipuncture sites, ecchymoses, petechiae, hematomas, vaginal bleeding, or hemorrhage from the gastrointestinal tract or genitourinary system.

Thrombotic manifestations occur less frequently than bleeding and include necrotic skin lesions, venous thromboembolism (deep vein thrombosis and pulmonary embolism), and acute arterial occlusions (stroke and myocardial infarction).

Pathophysiology

An understanding of the pathophysiology of DIC helps with understanding laboratory testing and management. The underlying disease (Box 40.5) stimulates the procoagulant system, which generates thrombin and results in consumption of coagulation factors and platelets. The fibrinolytic system also is activated, converting plasminogen to plasmin. Plasmin prevents stabilization of fibrin clots (resulting in circulating fibrin monomers) and degrades existing fibrin clots and fibrinogen-releasing cleavage products called D-dimers. The circulating fibrin monomers are soluble and thus form weak clots.

Laboratory Testing

Laboratory findings in suspected DIC vary, and no single laboratory test is diagnostic. Clinical findings must be interpreted along with laboratory data. Typical laboratory findings in DIC include thrombocytopenia, prolonged PT and aPTT, low levels of fibrinogen due to consumption, and increased levels of D-dimers and soluble fibrin monomer complexes.

Management

Principles of DIC management include identifying and treating the underlying disease while managing the coagulopathy.

Blood Component Replacement Therapy

Observation may be reasonable for patients who have low-grade compensated DIC with mild coagulopathy and no bleeding. However, for patients who have symptomatic hemorrhage or abnormal laboratory results and are at risk for bleeding, therapy includes transfusion of blood components (Box 40.6).

Ancillary Therapies

Although *UFH* inhibits thrombin and interrupts the cycle of consumptive coagulopathy, it is also associated with hemorrhage, including intracranial hemorrhage. Thus, in patients with acute DIC, heparin usually has a limited role. It may, however, have a role in chronic DIC as seen with solid tumors, the retained dead fetus syndrome, aortic aneurysm, and giant hemangiomas. *Recombinant activated protein C* has been shown to decrease the risk of death among patients with severe sepsis, but at present it is not widely used. *Antithrombin concentrate*

Box 40.6 • Blood Component Replacement Therapy for DIC

If fibrinogen level is low (<100 mg/dL), give cryoprecipitate.

If PT and aPTT are markedly prolonged (suggesting significant coagulation factor deficiency states), give fresh frozen plasma.

If the platelet count is low ($<30\times10^9$/L, or $<50\times10^9$/L for bleeding patients), give platelet concentrates (target platelet count 30×10^9/L after infusion, especially if the patient has active bleeding or is undergoing procedures).

Monitor transfusion therapy with CBC, PT, aPTT, and fibrinogen level 60 minutes after a transfusion and every 6-8 hours thereafter.

Abbreviations: aPTT, activated partial thromboplastin time; CBC, complete blood cell count; DIC, disseminated intravascular coagulation; PT, prothrombin time.

has not been shown to decrease the risk of death among patients with DIC. *Fibrinolysis inhibitors*, such as ε-aminocaproic acid or tranexamic acid, are generally contraindicated in DIC.

Acquired von Willebrand Syndrome

Acquired von Willebrand syndrome is an acquired quantitative or qualitative abnormality of vWF that is associated with monoclonal protein disorders, myeloproliferative disease, hypothyroidism, and other malignant processes. Occasionally no underlying disease is found. Management consists of treatment of the associated conditions and infusion of vWF concentrates to prevent and treat hemorrhage; desmopressin is seldom effective.

Key Definition

Acquired von Willebrand syndrome: *an acquired quantitative or qualitative abnormality of vWF associated with monoclonal protein disorders, myeloproliferative disease, hypothyroidism, and other malignant processes.*

Acquired (Autoimmune) Hemophilia

In acquired (autoimmune) hemophilia, the development of FVIII inhibitors in previously healthy people results in a potentially life-threatening bleeding disorder. Management consists of maintaining hemostasis with special factor concentrates (activated prothrombin complex concentrates, recombinant factor VIIa, or recombinant porcine FVIII) and immunosuppression (glucocorticoids, cytotoxic chemotherapy, and anti-CD20 antibody [rituximab]).

KEY FACTS

- ✓ Hepatocellular damage and liver failure—
  - decreased production of clotting factors (most are produced in the liver)
  - bleeding tendency
- ✓ DIC—suspect if patient has a condition known to predispose to DIC
- ✓ Acquired (autoimmune) hemophilia—development of FVIII inhibitors in a previously healthy person causes a potentially life-threatening bleeding disorder

Platelet Disorders

Platelets are produced in the bone marrow and, after circulating for 7 to 10 days, are destroyed in the reticuloendothelial system. Thrombocytopenia is most commonly acquired and poses a risk of bleeding. It commonly occurs as a result of decreased production or accelerated destruction. When thrombocytopenia occurs for the first time, the diagnosis of pseudothrombocytopenia should be excluded with examination of a peripheral blood smear. Rarely, thrombocytopenia is congenital.

Causes of Thrombocytopenia

Pseudothrombocytopenia is an in vitro phenomenon due to EDTA-induced platelet clumping; platelet count ranges from 50×10^9/L to 100×10^9/L. The CBC should be repeated with a blood sample collected in a citrate tube to prevent clumping. A peripheral blood smear (Figure 40.2) is useful to detect clumping.

After exclusion of pseudothrombocytopenia, other causes of thrombocytopenia are broadly classified as accelerated platelet destruction, decreased platelet production, or splenic sequestration (careful physical examination for splenomegaly will help exclude this possibility) (Box 40.7). Potentially serious causes of thrombocytopenia, which are typically associated with microvascular thrombosis rather than bleeding, should be excluded. These include heparin-induced thrombocytopenia (HIT), thrombotic thrombocytopenic purpura, catastrophic antiphospholipid antibody syndrome, and pregnancy-associated HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count).

Abnormally large platelets (Figure 40.3) are seen in immune thrombocytopenia, clonal myeloid disorders (eg, essential thrombocythemia), and congenital disorders of platelet synthesis and function (eg, conditions associated with mutations of the *MYH9* gene [eg, May-Hegglin anomaly] and Bernard-Soulier syndrome).

Thrombocytopenia Due to Increased Platelet Destruction

Autoimmune Thrombocytopenic Purpura

Autoimmune thrombocytopenic purpura, formerly called idiopathic thrombocytopenic purpura, is an autoimmune

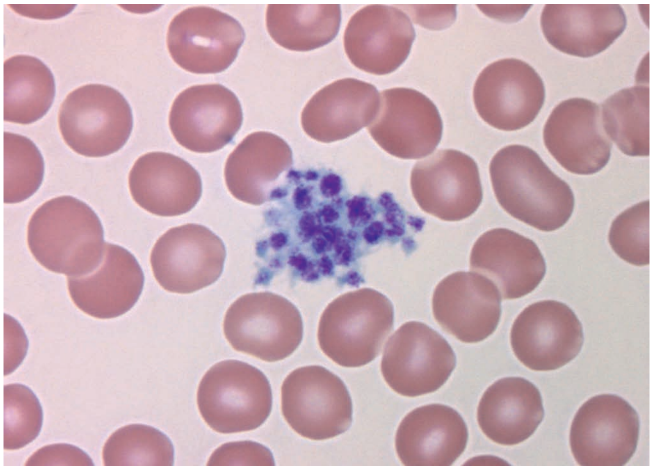

Figure 40.2. *Platelet Clumping (Agglutination). Agglutination is a cause of artifactual thrombocytopenia (pseudothrombocytopenia). Drawing the blood in a citrate tube rather than an EDTA-anticoagulated tube usually eliminates this in vitro phenomenon (Wright-Giemsa).*

(Courtesy of Curtis A. Hanson, MD, Mayo Clinic, Rochester, Minnesota; used with permission.)

Box 40.7 • Causes of Thrombocytopenia

- Pseudothrombocytopenia
- Dilutional
  - Massive transfusion
  - Pregnancy
- Increased destruction
  - Immune
    - Autoimmune
    - Idiopathic
    - Secondary (drug-induced or connective tissue diseases)
  - Nonimmune
    - Consumptive (DIC)
    - Sepsis
- Decreased production
  - Bone marrow failure syndromes
    - Primary: anaplastic anemia
    - Secondary: metastatic disease, hematologic cancers
  - Nutritional
    - Vitamin B_{12} or folate deficiency
  - Infections
    - Viral (HIV infection, CMV infection, viral hepatitis)

Abbreviations: CMV, cytomegalovirus; DIC, disseminated intravascular coagulation.

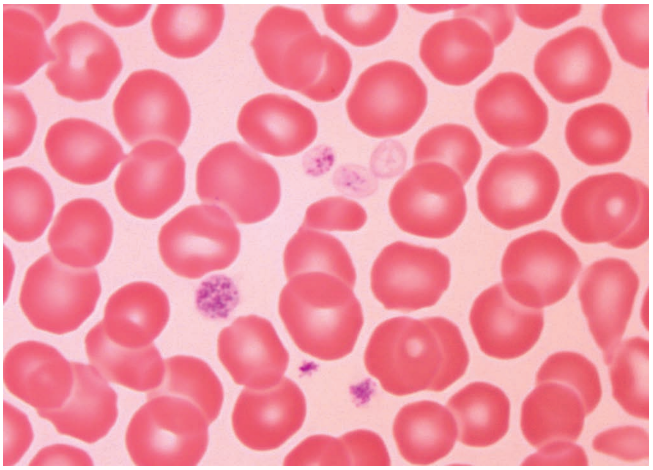

Figure 40.3. *Giant Platelets. Giant platelets may be associated with congenital platelet synthesis disorders, acquired clonal myeloid disorders, or immune thrombocytopenia (Wright-Giemsa).*

(Courtesy of Curtis A. Hanson, MD, Mayo Clinic, Rochester, Minnesota; used with permission.)

disease characterized by thrombocytopenia, usually with a normal white blood cell count and hemoglobin concentration (Table 40.3).

The diagnosis of autoimmune thrombocytopenic purpura is a diagnosis of exclusion (Box 40.8).

Clinical Manifestations

In adults, autoimmune thrombocytopenic purpura is often diagnosed from an incidental finding on routine CBC or from

Table 40.3 • Autoimmune Thrombocytopenic Purpura

Characteristic	**Acute**	**Chronic**
Presentation	Abrupt onset of petechiae, purpura, mucosal bleeding	Insidious petechiae, menorrhagia
Usual age	Children (2-6 y)	Adults (20-40 y)
Female to male ratio	1:1	3:1
Antecedent infection	Common (85%) Typically an upper respiratory tract infection	Uncommon
Platelet count, $\times 10^9$/L	<20	30-80
Duration	2-6 wk	Months to years
Spontaneous remission	80% within 6 mo	Uncommon, fluctuates

Data from Liel MS, Recht M, Calverley DC. Thrombocytopenia caused by immunologic platelet destruction. In: Greer JP, Arber DA, Glader B, List AF, Means RT Jr, Paraskevas F, et al, editors. 13th ed. Wintrobe's clinical hematology. Philadelphia (PA): Lippincott Williams & Wilkins; c2014. p. 1061-76.

Box 40.8 • Diagnosis of Autoimmune Thrombocytopenic Purpura

- Examine a peripheral blood smear to exclude microangiopathy.
- In mild to moderate thrombocytopenia, exclude congenital causes of thrombocytopenia, such as type 2B von Willebrand disease and other macrothrombocytopenias, which are typically associated with a lifelong personal and family history of bleeding and bruising.
- Evaluate for heavy alcohol use and drugs associated with thrombocytopenia.
- Test for HIV infection and hepatitis C in patients with risk factors.

Box 40.9 • American Society of Hematology Guidelines for Treatment of Autoimmune Thrombocytopenic Purpura

- Patients with platelet counts ≥50×10^9/L do not routinely require treatment.
- Patients with platelet counts between 30×10^9/L and 50×10^9/L should be treated if they have mucous membrane bleeding or risk factors for bleeding, including hypertension, peptic ulcer disease, or a vigorous lifestyle.
- Patients with platelet counts <30×10^9/L (with or without bleeding) should be treated.
  - Prednisone is the mainstay of initial treatment; initially, 70% of patients respond, with a 40% chance of long-term remission (prednisone 1 mg/kg daily for up to 1 month; then a tapering schedule).
  - If bleeding is severe, treat with intravenous immunoglobulin (1 g/kg daily for 2 days) and platelets; high-dose intravenous corticosteroids can also be considered (eg, methylprednisolone, 1 g daily for 2-3 consecutive days; initial response rate, 80%).

an initial bleeding episode (eg, petechiae and purpura, mucous membrane hemorrhage, or cerebromeningeal bleeding). Up to 60% of adults have disease progression to a chronic state of autoimmune thrombocytopenic purpura. The possibility of splenomegaly should be investigated, but it is seen in only 10% of patients. If splenomegaly is present, the thrombocytopenia is due to platelet sequestration in the spleen.

Laboratory Findings

In most patients, the platelet count is less than 50×10^9/L; in 30%, it is less than 10×10^9/L (spontaneous bleeding may occur at this level). The mean platelet volume is increased. Antibodies to specific platelet-membrane glycoproteins, usually the glycoprotein IIb/IIIa complex, and platelet-associated immunoglobulin G can be detected in most patients but are not necessary for diagnosis or treatment.

In patients older than 60 years, bone marrow examination is appropriate to rule out another disorder causing thrombocytopenia (eg, a myelodysplastic syndrome or lymphoma). Bone marrow examination in autoimmune thrombocytopenic purpura shows a normal to increased number of megakaryocytes.

Treatment

The American Society of Hematology guidelines for treatment are shown in Box 40.9.

Splenectomy, the treatment of choice for corticosteroid-refractory autoimmune thrombocytopenic purpura, removes the predominant site of antibody production and platelet destruction; the likelihood of remission is 75%, with about 60% of patients remaining in long-term remission. Pneumococcal, meningococcal, and *Haemophilus influenzae* vaccines should be administered 2 weeks before splenectomy. The absence of Howell-Jolly bodies on a postsplenectomy peripheral blood smear suggests the presence of an accessory spleen, and accessory splenectomy can result in remission. Pulsed dexamethasone (40 mg daily for 4 sequential days, every 28 days, for 4-6 months) is an option for the treatment of resistant autoimmune thrombocytopenic purpura or disease relapse. Novel agents approved for use in patients with corticosteroid-refractory autoimmune thrombocytopenic purpura include oral (eltrombopag) and parenteral (romiplostim) thrombopoietin receptor agonists. Other agents used in refractory cases include azathioprine, cyclophosphamide, colchicine, cyclosporine, rituximab, vincristine, vinblastine, anti-Rh_{O}(D) immune globulin, danazol, and immunoadsorption apheresis on staphylococcal protein A columns.

Drug-Induced Thrombocytopenia

Drug-induced thrombocytopenia is caused by direct marrow toxicity or by haptens bound to a carrier protein. Common causative drugs include heparin, quinidine, quinine, valproic acid, gold, trimethoprim-sulfamethoxazole, amphotericin B, carbamazepine, chlorothiazide, chlorpropamide, procainamide, rifampin, and vancomycin. Glycoprotein IIb/IIIa antagonists have also been implicated. Heparin causes one of the most lethal drug-induced thrombocytopenias, HIT.

Drug-induced thrombocytopenia subsides in 4 to 14 days after use of the drug is discontinued—except for gold-induced thrombocytopenia, which may take much longer. In contrast, viral-induced thrombocytopenia resolves in 2 weeks to 3 months.

Heparin-Induced Thrombocytopenia

Type I HIT is a benign, nonimmune-mediated thrombocytopenia that occurs in association with UFH, typically in the first 4 days of heparin therapy. *Type II HIT* is a more serious, immune-mediated thrombocytopenia.

The incidence of HIT is 1% to 8% with UFH; the incidence is lower with low-molecular-weight heparin. HIT can develop at any dose of heparin, including low-dose prophylaxis for venous

Box 40.10 • Onset of Thrombocytopenia in Heparin-Induced Thrombocytopenia

Typical: 4-14 days after initiating heparin administration

Rapid: <4 days in patients with recent (≤3 months) heparin exposure

Delayed: 2-3 weeks after discontinuation of heparin administration

thrombosis postoperatively. The onset of thrombocytopenia varies (Box 40.10).

The platelet count decreases 50% from baseline (ie, from before heparin administration). Thrombosis may or may not occur and may be venous (more commonly) or arterial. Laboratory testing includes functional assays (serotonin release assay) and antigen assays (heparin-dependent antibody against platelet factor 4).

Immunoglobulin G antibodies to platelet factor 4–heparin complexes result in platelet activation, generation of thrombin, and a high risk of thrombosis. Rare complications are listed in Box 40.11.

Anticoagulant management involves administering a parenteral direct thrombin inhibitor (bivalirudin or argatroban) (Box 40.12). Argatroban is the treatment of choice for patients with renal insufficiency because of its hepatic elimination; in contrast, for patients with hepatic failure, bivalirudin (which is renally excreted) is an option (lepirudin is no longer marketed).

Chemotherapy-Associated Thrombocytopenia

The threshold for platelet transfusion is 10×10^9/L unless other risk factors for bleeding (eg, fever or mucosal lesion) are present. Interleukin 11 (oprelvekin) is modestly effective but is associated with fluid retention and atrial dysrhythmias. Pharmacologic agents stimulating the thrombopoietin receptor have been approved for clinical use.

Thrombocytopenia Due to Decreased Platelet Production

Thrombocytopenia caused by decreased platelet production typically occurs as a result of disorders affecting the bone marrow. These can be broadly classified as shown in Box 40.13. Management consists of identifying and treating the underlying disease.

Box 40.11 • Rare Complications of Heparin-Induced Thrombocytopenia

Warfarin-induced venous gangrene with limb damage

Acute platelet activation syndromes (fever, chills, or transient amnesia) 5-30 minutes after an intravenous bolus of heparin

Painful, necrotic skin lesions at the site of the heparin injection

Box 40.12 • *Do*'s and *Don't*'s of HIT

Do promptly stop all use of heparin (UFH and LMWH), including line flushes and heparin-impregnated catheters, if HIT is clinically suspected

Do administer a DTI (eg, bivalirudin or argatroban)

Do record heparin as an allergy for patients with HIT

Do not switch to LMWH; the antibody has high cross-reactivity with an LMWH–platelet factor 4 complex

Do not administer warfarin until the platelet count increases to approximately $100\text{-}150\times10^9$/L

Do not administer warfarin without bridging with a DTI

Abbreviations: DTI, direct thrombin inhibitor; HIT, heparin-induced thrombocytopenia; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

Congenital Platelet Disorders

Congenital abnormalities of the platelet receptor glycoproteins lead to platelet dysfunction and thrombocytopenia. Lifelong mucocutaneous bleeding and postoperative bleeding are typical. Platelet transfusions are used for prevention and treatment of hemorrhage. A risk of frequent transfusions is platelet alloimmunization. Diagnosis is based on platelet function testing (Box 40.14).

Thrombocytopenia in Pregnancy

Mild thrombocytopenia (platelet count $>70\times10^9$/L) occurs in 6% to 8% of pregnant women at term and in 25% of women with preeclampsia. The most common causes of thrombocytopenia in pregnancy are physiologic gestational thrombocytopenia and nonphysiologic benign gestational thrombocytopenia, which account for 75% of cases. No treatment is required. Platelet counts generally recover within 72 hours after delivery

Box 40.13 • Disorders That Decrease Platelet Production in the Bone Marrow

Primary marrow or metastatic cancer (eg, solid tumor, leukemia or lymphoma)

Infections (eg, HIV infection, cytomegalovirus infection, sepsis, or viral hepatitis)

Inflammatory or autoimmune states (eg, connective tissue diseases such as systemic lupus erythematosus or rheumatoid arthritis)

Nutritional deficiencies (eg, vitamin B_{12} or folate deficiencies)

Bone marrow failure states (eg, myelodysplastic syndrome or aplastic anemia)

Box 40.14 • Diagnosis of Congenital Platelet Disorders

Bernard-Soulier syndrome
  Due to abnormalities in the glycoprotein Ib/IX complex receptor
  Characterized by large platelets
  Platelet aggregation is decreased with ristocetin but normal with adenosine diphosphate, epinephrine, collagen, and arachidonate
Glanzmann thrombasthenia
  Due to abnormalities in the glycoprotein IIb/IIIa complex
  Platelet aggregation is normal with ristocetin but decreased with adenosine diphosphate, epinephrine, collagen, and arachidonate
Wiskott-Aldrich syndrome
  Associated with small platelets

without adverse maternal or fetal outcomes. The diagnosis is one of exclusion.

Other common causes include preeclampsia (including HELLP syndrome), idiopathic autoimmune thrombocytopenia (or autoimmune thrombocytopenic purpura), DIC, acute fatty liver of pregnancy, HIV infection, antiphospholipid antibodies, drugs (quinine, quinidine, cocaine, or heparin), nutritional deficiency, and thrombotic thrombocytopenic purpura. The primary treatment of HELLP syndrome is stabilization of the patient's condition and delivery of the fetus.

KEY FACTS

- ✓ Pseudothrombocytopenia—caused by in vitro EDTA-induced platelet clumping
- ✓ Autoimmune thrombocytopenic purpura—usually leukocyte count and hemoglobin concentration are normal
- ✓ Splenectomy—treatment of choice for corticosteroid-refractory autoimmune thrombocytopenic purpura
- ✓ Drug-induced thrombocytopenia—caused by direct marrow toxicity or by haptens bound to a carrier protein
- ✓ Type I HIT—
  - benign, nonimmune-mediated thrombocytopenia
  - occurs with use of UFH, typically in first 4 days of heparin therapy
- ✓ Type II HIT—serious, immune-mediated thrombocytopenia
- ✓ Thrombocytopenia in pregnancy—
  - mild (platelet count $>70\times10^9$/L)
  - occurs in 6%-8% of pregnant women at term
  - occurs in 25% of women with preeclampsia

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Malignant Hematologic Disorders

CARRIE A. THOMPSON, MD

Hematologic Neoplasms

There are 4 types of hematologic neoplasms:

1. Lymphoproliferative disorders—chronic lymphocytic leukemia (CLL) (Box 41.1), hairy cell leukemia (HCL), large granular lymphocyte (LGL) leukemia (Box 41.2), Hodgkin lymphoma (Box 41.3), and non-Hodgkin lymphoma (NHL)
2. Plasma cell disorders—monoclonal gammopathies of undetermined significance (MGUS), multiple myeloma, Waldenström macroglobulinemia, light chain amyloidosis, and plasmacytoma
3. Acute leukemias—acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL)
4. Chronic myeloid disorders—myelodysplastic syndromes (MDSs), chronic myeloid leukemia (CML), and myeloproliferative neoplasms

Lymphoproliferative Disorders

The risk of lymphoproliferative disorders is increased for immunocompromised patients, including those receiving immunosuppressive medications for autoimmune diseases or solid organ transplant and those with HIV infection.

Chronic Lymphocytic Leukemia

CLL is a clonal disorder of mature lymphocytes (Figure 41.1) that is primarily seen in older patients (median age, 65-70 years). Median survival is about 10 years.

The diagnosis of CLL requires a B-lymphocyte count of more than 5.0×10^9/L; a smaller B-cell clone is also considered CLL if accompanied by lymphadenopathy, splenomegaly, marrow infiltration, or cytopenias attributable to CLL. A small B-cell clone may be detected incidentally by flow cytometry in about 5% of patients older than 60 years without accompanying cytopenias, adenopathy, or splenomegaly; these patients have monoclonal B-cell lymphocytosis and should be observed.

The peripheral blood smear in CLL classically shows *smudge cells*, which are lymphocytes that break apart during slide processing (Figure 41.1). Interphase fluorescence in situ hybridization testing identifies the characteristic CLL immunophenotype: clonal light-chain expression, $CD5^+$ (also expressed in mantle cell lymphoma), $CD19^+$, $CD23^+$, and $CD20^+$. The 2 widely used staging classifications are shown in Tables 41.1 and 41.2.

Recurrent infections are a common complication, in part because of hypogammaglobulinemia. Prophylactic γ-globulin may reduce infection rates and should be considered for patients with recurrent serious infections. About 5% of patients have autoimmune hematologic complications, including hemolytic anemia, thrombocytopenia, and pure red cell aplasia. Patients with CLL also are at increased risk for second malignant processes, including evolution to a more aggressive B-cell lymphoma (ie, *Richter transformation*), skin cancer, and solid organ cancers. If patients with CLL have fever, it is important to exclude infection and transformation to diffuse large B-cell lymphoma (DLBCL) before attributing the fever to progressive CLL.

For patients with early-stage CLL, the standard practice is observation. Indications to begin treatment include cytopenias, progressive adenopathy or splenomegaly, constitutional symptoms, or rapid lymphocyte doubling time. Chemotherapy in combination with immunotherapy, including a purine analogue (fludarabine or pentostatin) plus rituximab (an anti-CD20 monoclonal antibody), is the initial treatment of choice for most patients. The major adverse effects of chemoimmunotherapy are myelosuppression and immunosuppression, which predispose the patient to infection.

Box 41.1 • WHO Classification of the Mature B-Cell Neoplasms (2008)

- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- Splenic lymphoma/leukemia, unclassifiable[a]
  - Splenic diffuse red pulp small B-cell lymphoma[a]
  - Hairy cell leukemia-variant[a]
- Lymphoplasmacytic lymphoma
- Waldenström macroglobulinemia
- Heavy chain diseases
  - Alpha heavy chain disease
  - Gamma heavy chain disease
  - Mu heavy chain disease
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
- Pediatric nodal marginal zone lymphoma[a]
- Follicular lymphoma
- Pediatric follicular lymphoma[a]
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
- DLBCL, NOS
  - T-cell/histiocyte-rich large B-cell lymphoma
  - Primary DLBCL of the central nervous system
  - Primary cutaneous DLBCL, leg type
  - EBV-positive DLBCL of the elderly[a]
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK-positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

Abbreviations: ALK, anaplastic lymphoma kinase; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; HHV8, human herpesvirus 8; NOS, not otherwise specified; WHO, World Health Organization.

[a] Provisional entities for which the WHO Working Group felt there was insufficient evidence to recognize as distinct diseases at this time.

Modified from Jaffe ES, Harris NL, Stein H, Isaacson PG. Classification of lymphoid neoplasms: the microscope as a tool for disease discovery. Blood. 2008 Dec 1;112(12):4384-99; used with permission.

Box 41.2 • WHO Classification of the Mature T-Cell and NK-Cell Neoplasms (2008)

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocyte leukemia
- Chronic lymphoproliferative disorder of NK cells[a]
- Aggressive NK cell leukemia
- Systemic EBV-positive T-cell lymphoproliferative disease of childhood
- Hydroa vacciniforme–like lymphoma
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous $CD30^+$ T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous γ-δ T-cell lymphoma
- Primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma[a]
- Primary cutaneous $CD4^+$ small/medium T-cell lymphoma[a]
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, ALK-positive
- Anaplastic large cell lymphoma, ALK-negative

Abbreviations: ALK, anaplastic lymphoma kinase; EBV, Epstein-Barr virus; NK, natural killer; NOS, not otherwise specified; WHO, World Health Organization.

[a] Provisional entities for which the WHO Working Group felt there was insufficient evidence to recognize as distinct diseases at this time.

Modified from Jaffe ES, Harris NL, Stein H, Isaacson PG. Classification of lymphoid neoplasms: the microscope as a tool for disease discovery. Blood. 2008 Dec 1;112(12):4384-99; used with permission.

Box 41.3 • WHO Classification of Hodgkin Lymphoma (2008)

- Nodular lymphocyte-predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
    - Nodular sclerosis classical Hodgkin lymphoma
    - Lymphocyte-rich classical Hodgkin lymphoma
    - Mixed cellularity classical Hodgkin lymphoma
    - Lymphocyte-depleted classical Hodgkin lymphoma

Abbreviation: WHO, World Health Organization.

Modified from Jaffe ES, Harris NL, Stein H, Isaacson PG. Classification of lymphoid neoplasms: the microscope as a tool for disease discovery. Blood. 2008 Dec 1;112(12):4384-99; used with permission.

Hairy Cell Leukemia

HCL is a rare mature B-cell neoplasm characterized by an insidious onset of cytopenias and the presence of cells with "hairy" cytoplasmic projections. The male to female ratio is 4:1 (Figure 41.2).

The symptoms are related to cytopenias, infections, and splenomegaly. The bone marrow often yields a "dry tap" (ie, no liquid marrow is obtained); core biopsy specimens are hypercellular, with diffuse infiltration by neoplastic cells and fibrosis. With treatment, most patients have a near-normal life span. HCL causes immunosuppression and increases the risk of infection. Atypical mycobacterial infections are a classic association.

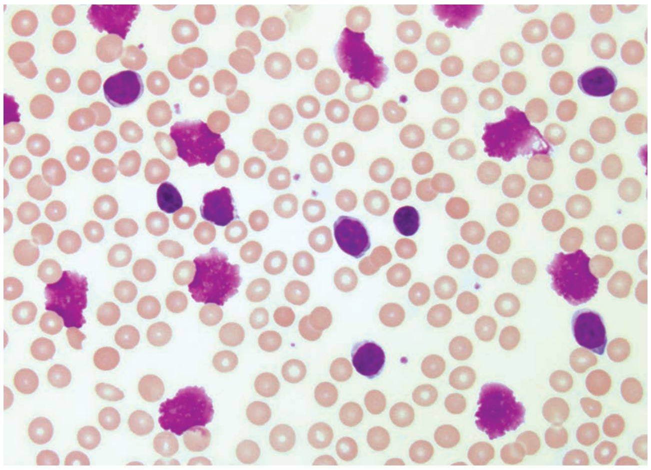

Figure 41.1. Chronic Lymphocytic Leukemia. Many small and mature lymphocytes have nuclei approximately the same size as red blood cells. Smudge cells are also characteristic of this disorder (peripheral blood smear; Wright-Giemsa).

(Courtesy of Curtis A. Hanson, MD, Mayo Clinic, Rochester, Minnesota; used with permission.)

Table 41.1 • Staging of Chronic Lymphocytic Leukemia: Rai Classification

Stage	Characteristics	Median Survival Time, mo
0	Peripheral lymphocytosis (>15×10^9/L), bone marrow lymphocytosis (>40%)	>150
I	Lymphocytosis, lymphadenopathy	101
II	Lymphocytosis, splenomegaly	71
III	Lymphocytosis, anemia (hemoglobin <11 g/dL), excluding AIHA	19
IV	Lymphocytosis, thrombocytopenia	19

Abbreviation: AIHA, autoimmune hemolytic anemia.

Data from Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. Blood. 1975 Aug;46(2):219-34.

LGL Leukemia

LGLs are cytotoxic T cells or natural killer cells (Figure 41.3); clonal expansion of LGLs is called LGL leukemia. T-cell LGL leukemia is associated with neutropenia, splenomegaly, and anemia. It occurs most commonly in older patients (median age, 60 years). Up to one-third of patients with T-cell LGL leukemia have rheumatoid arthritis, and there is overlap with Felty syndrome (ie, triad of neutropenia, rheumatoid arthritis, and splenomegaly). The diagnosis is suggested by flow cytometry and can be confirmed by T-cell-receptor gene rearrangement studies.

T-cell LGL leukemia is a chronic disorder that requires treatment only if symptoms are present. Immunosuppressive therapy with methotrexate, cyclophosphamide, or cyclosporine is often effective.

Hodgkin Lymphoma

Treatment of Hodgkin lymphoma is a major success of modern cancer therapy. With treatment, more than 85% of patients with Hodgkin lymphoma are now cured.

Table 41.2 • Staging of Chronic Lymphocytic Leukemia: International Workshop on Chronic Lymphocytic Leukemia Classification

Clinical Stage	Features
A	No anemia or thrombocytopenia and <3 areas of lymphoid enlargement (spleen, liver, and lymph nodes in cervical, axillary, and inguinal regions)
B	No anemia or thrombocytopenia, but ≥3 involved areas of lymphoid enlargement
C	Anemia (hemoglobin <10 g/dL) or thrombocytopenia (or both)

Data from International Workshop on CLL. Chronic lymphocytic leukaemia: proposals for a revised prognostic staging system. Br J Haematol. 1981 Jul;48(3):365-7.

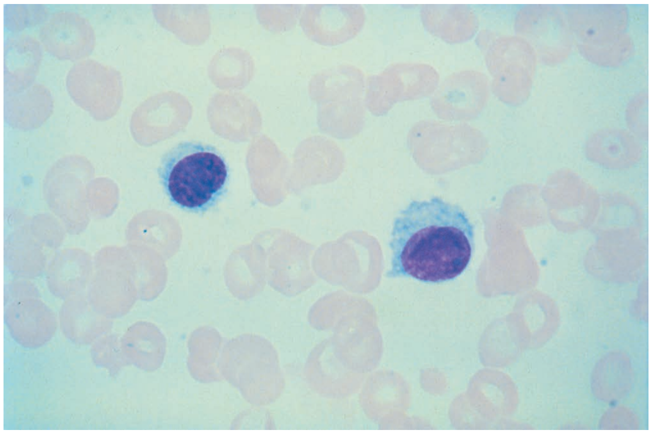

Figure 41.2. *Hairy Cell Leukemia. These mature lymphocytes have eccentrically placed nuclei, pale cytoplasm, and characteristic projections (bone marrow aspirate smear; Wright-Giemsa).*

The age at presentation has a bimodal distribution, with the first peak at a median age of 25 years and the second peak after age 60 years. Hodgkin lymphoma usually presents with locally limited disease. The typical finding at presentation is lymphadenopathy; less common presentations include pruritus, cytopenias, and pain in involved lymph nodes after alcohol consumption.

The diagnosis of Hodgkin lymphoma is based on the presence of Reed-Sternberg cells, which typically have 2 or more nuclei with prominent nucleoli that give the cells the appearance of owl eyes (Figure 41.4).

Disease stage (Table 41.3) is the principal factor in selecting treatment. The disease is routinely staged with the use of positron emission tomography. Currently, the treatment of choice for localized disease is a short course of combination chemotherapy

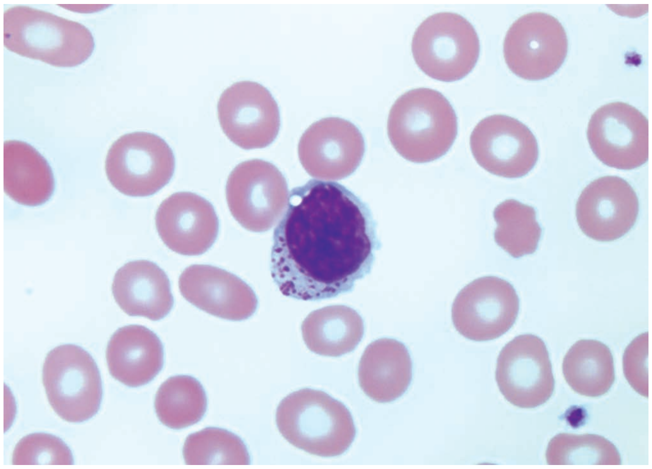

Figure 41.3. *Large Granular Lymphocyte. The pale blue cytoplasm contains azurophilic granules (peripheral blood smear; Wright-Giemsa).*

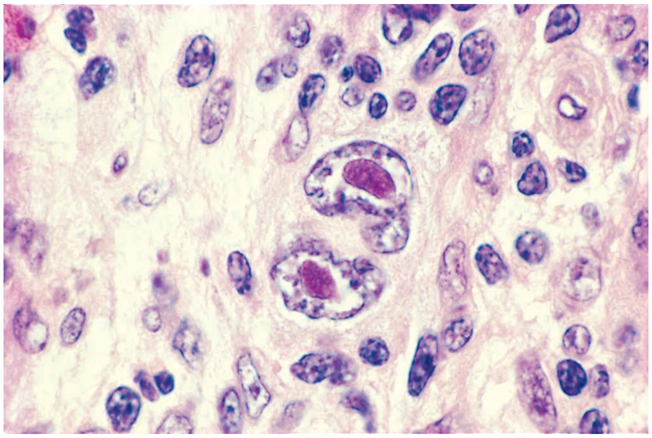

Figure 41.4. *Hodgkin Lymphoma. A Reed-Sternberg cell, the large binuclear cell, is present (bone marrow biopsy section; hematoxylin-eosin).*

(Courtesy of Curtis A. Hanson, MD, Mayo Clinic, Rochester, Minnesota; used with permission.)

Table 41.3 • The Lugano Classification of Hodgkin Lymphoma[a]

Stage	Involvement	Extranodal Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II Bulky[b]	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

[a] Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologic findings. Tonsils, Waldeyer tonsillar ring, and spleen are considered nodal tissue.

[b] Whether stage II bulky disease is treated as limited or advanced disease may be determined by histologic findings and several prognostic factors.

From Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al; Alliance, Australasian Leukaemia and Lymphoma Group; Eastern Cooperative Oncology Group; European Mantle Cell Lymphoma Consortium; Italian Lymphoma Foundation; European Organisation for Research; Treatment of Cancer/Dutch Hemato-Oncology Group; Grupo Español de Médula Ósea; German High-Grade Lymphoma Study Group; German Hodgkin's Study Group; Japanese Lymphorra Study Group; Lymphoma Study Association; NCIC Clinical Trials Group; Nordic Lymphoma Study Group; Southwest Oncology Group; United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014 Sep 20;32(27):3059-68; used with permission.

with ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine) and low doses of radiotherapy. Most patients with localized disease are cured. The treatment of choice for advanced disease is combination chemotherapy; cure rates are up to 65%. Autologous stem cell transplant is considered for relapses after chemotherapy.

Late complications of Hodgkin lymphoma therapy are substantial. They include infertility, premature menopause, hypothyroidism, cardiomyopathy, coronary artery disease, pulmonary fibrosis, and secondary malignant processes such as AML, MDS, NHL, and solid tumors (eg, breast, lung, and thyroid cancer, if those areas are included in the irradiated field).

KEY FACTS

- ✓ Risk of lymphoproliferative disorders—increased for immunocompromised patients, such as those infected with HIV or receiving immunosuppressive agents for autoimmune diseases or solid organ transplant
- ✓ Peripheral blood smear in CLL—smudge cells (lymphocytes that break apart during slide processing)
- ✓ CLL—increases the risk of second cancers (eg, more aggressive B-cell lymphoma, skin cancer, and solid organ cancers)
- ✓ Hodgkin lymphoma—
  - cure rate >85%
  - typical presentation: lymphadenopathy
  - less common presentations: pruritus, cytopenias, pain in lymph nodes after alcohol consumption
- ✓ Late complications of Hodgkin lymphoma therapy—
  - infertility, premature menopause, hypothyroidism
  - cardiomyopathy, coronary artery disease
  - pulmonary fibrosis
  - secondary malignant processes: AML, MDS, NHL, and solid tumors (in areas included in the irradiated field)

Non-Hodgkin Lymphomas

NHL is a diverse group of lymphoproliferative disorders. The Ann Arbor Staging System has traditionally been used for NHL. Stage I indicates cancer in a single region; stage II indicates cancer in 2 regions but on the same side of the diaphragm; stage III indicates cancer on both sides of the diaphragm; and stage IV indicates diffuse disease.

Low-Grade (Indolent) Lymphomas

Low-grade (indolent) lymphomas may remain in a chronic phase for many years or transform into aggressive lymphomas. Patients with follicular lymphoma, the most common type of indolent lymphoma, often have a t(14;18) translocation resulting in amplification of the antiapoptotic *BCL2* gene.

Low-grade NHLs are not curable unless they are stage I disease, which can sometimes be cured with radiotherapy. At diagnosis, most patients have stage III or IV disease, which is not curable; however, median survival is variable and now exceeds 10 years. Observation is an option for asymptomatic patients with no evidence of bulky disease. Treatment is indicated for patients with symptoms, bulky disease, or cytopenias. Many therapeutic regimens exist, including bendamustine with rituximab, CVP (cyclophosphamide, vincristine, and prednisone) with rituximab; rituximab alone; R-CHOP (rituximab, cyclophosphamide, hydroxydaunomycin [Adriamycin], vincristine [Oncovin], and prednisone); and fludarabine.

Gastric mucosa–associated lymphoid tissue (MALT) lymphomas are associated with *Helicobacter pylori* infections. Up to 70% of patients respond to a regimen of antibiotics in combination with a proton pump inhibitor. If this is unsuccessful, chemotherapy or irradiation is typically used.

Aggressive Lymphomas

In contrast to low-grade lymphomas, aggressive lymphomas are potentially curable, but the duration of survival is short if remission is not achieved. At initial evaluation, patients typically have symptomatic disease, including B symptoms (fevers, drenching night sweats, and weight loss) (Table 41.3).

The most common aggressive lymphoma is DLBCL. Standard therapy is R-CHOP chemotherapy. For patients with aggressive lymphoma that relapses after complete remission, autologous stem cell transplant is the standard therapy. The International Prognostic Factor Index uses age, lactate dehydrogenase level, performance status scores, disease stage, and extranodal involvement to predict survival of patients who have DLBCL. The 5-year survival rate ranges from 26% to 73%, depending on risk factors.

Mantle cell lymphoma is characterized by a $CD5^+$ and $CD20^+$ immunophenotype and a t(11;14) translocation, with overexpression of the cyclin D1 oncogene. Patients may have gastrointestinal tract involvement (ie, *lymphomatous polyposis*). Unlike other aggressive lymphomas, mantle cell lymphoma is not curable.

Very aggressive lymphomas, such as Burkitt lymphoma and lymphoblastic lymphoma, are treated with regimens similar to those used for ALL. These subtypes carry a high risk of central nervous system involvement and tumor lysis syndrome.

Plasma Cell Disorders (Monoclonal Gammopathies)

The plasma cell disorders (monoclonal gammopathies) are characterized by clonal proliferation of plasma cells, usually associated with the presence of monoclonal immunoglobulins (M proteins) in the serum or urine (or both).

Monoclonal Gammopathies of Undetermined Significance

In MGUS, the most common form of dysproteinemia, the serum M protein level is low (typically <3 g/dL) and the bone marrow has less than 10% plasma cells. The serum creatinine, calcium, and hemoglobin levels are within the reference ranges, and the urine has either no M protein or only a small amount. Osteolytic bone lesions are absent, and patients are usually asymptomatic.

MGUS is common—an M protein is present in the serum in 5% of persons older than 70 years. MGUS progresses to a malignant monoclonal gammopathy at an annual rate of about 1%. Patients with MGUS should be observed.

Multiple Myeloma

The median age at onset of multiple myeloma is 65 years. It is more common in men and in African Americans. By definition, patients must have 10% or more clonal plasma cells in the bone marrow (Figure 41.5), an M protein in the serum or urine, and signs of end-organ damage that are thought to be related to the plasma cell proliferative disorder (mnemonic, *CRAB*: calcium [ie, hypercalcemia], renal failure, anemia, and bone lesions [osteolytic]). The presence of more than 10% clonal plasma cells in the bone marrow without end-organ damage or symptoms is called "smoldering" multiple myeloma.

Clinical features of multiple myeloma include fatigue, bone pain, anemia, renal insufficiency, hypercalcemia, and spinal cord compression. A peripheral blood smear may show rouleaux.

The median survival has improved with newer treatments. The International Staging System for Multiple Myeloma is useful for prognostication, with median survival ranging from 29 to 62 months (Table 41.4).

Therapy for fit patients involves "induction" of a response with dexamethasone in combination with lenalidomide and bortezomib, followed by autologous stem cell transplant. For patients who are older or who have poor performance status, lenalidomide and dexamethasone is a reasonable treatment. Palliative radiotherapy is effective in managing bone pain. Bisphosphonate therapy delays the onset of skeletal-related events and decreases bone pain. The most worrisome adverse effect of bisphosphonate therapy is osteonecrosis of the jaw.

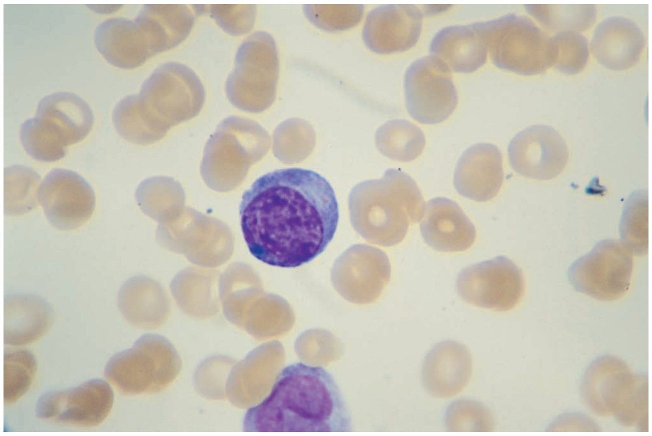

Figure 41.5. *Plasma Cell. The round nucleus is eccentrically placed; the copious, dark blue cytoplasm has a characteristic pale-staining area adjacent to the nucleus (bone marrow aspirate smear; Wright-Giemsa).*

Table 41.4 • International Staging System for Multiple Myeloma

Stage	Serum β_2-Microglobulin, mg/L	Serum Albumin, g/dL	Median Survival, mo
I	<3.5	≥3.5	62
II	3.5-5.5	<3.5	44
III	>5.5	. . .	29

Modified from Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Blade J, et al. International staging system for multiple myeloma. J Clin Oncol. 2005 May 20;23(15):3412-20. Epub 2005 Apr 4. Erratum in: J Clin Oncol. 2005 Sep 1;23(25):6281. Harousseau, Jean-Luc [corrected to Avet-Loiseau, Herve]; used with permission.

KEY FACTS

- ✓ Gastric MALT lymphoma—
  - associated with *H pylori* infection
  - therapy: antibiotics with proton pump inhibitor (70% response rate)
- ✓ DLBCL—
  - most common aggressive lymphoma
  - R-CHOP chemotherapy
- ✓ MGUS—
  - progression to malignant monoclonal gammopathy (annual rate 1%)
  - observation
- ✓ *CRAB* (mnemonic for multiple myeloma)—
  - calcium (ie, hypercalcemia)
  - renal failure
  - anemia
  - bone lesions (osteolytic)

Waldenström Macroglobulinemia

Waldenström macroglobulinemia is characterized by an immunoglobulin M paraprotein, clonal lymphoplasmacytic cells in the bone marrow, and anemia, hyperviscosity, lymphadenopathy, or hepatosplenomegaly. Bence Jones proteinuria may be present, and hyperviscosity syndrome occurs in 15%.

Hyperviscosity syndrome is characterized by fatigue, dizziness, blurred vision, bleeding, sausage-shaped retinal veins, and papilledema. The initial treatment of hyperviscosity is plasmapheresis followed by chemotherapy. Active drugs include rituximab, alkylating agents, and purine nucleoside analogues such as fludarabine.

Amyloidosis

The **amyloidoses** (Box 41.4) comprise a group of diseases that are characterized by extracellular deposition of insoluble fibrillar proteins that stain with Congo red.

Key Definition

Amyloidoses: *diseases characterized by extracellular deposition of insoluble fibrillary proteins that stain with Congo red.*

The amyloid fibrils in AL amyloidosis are fragments of immunoglobulin light chains. The bone marrow usually has less than 20% plasma cells, and there are no lytic bone lesions. Initial biopsies should include fat aspiration of the abdominal wall (80% positive) and bone marrow biopsy (50% positive).

Patients with AL amyloidosis may have fatigue, weight loss, hepatomegaly, macroglossia, renal insufficiency, nephrotic syndrome, congestive heart failure, orthostatic hypotension, carpal tunnel syndrome, or peripheral neuropathy. When patients have cardiac involvement, electrocardiography may show low voltage or Q waves. The echocardiogram is abnormal in 60%, showing concentrically thickened ventricles or a thickened interventricular septum and sometimes a speckled appearance. Peripheral neuropathy is often associated with autonomic failure, as manifested by diarrhea, pseudo-obstruction of the bowel, or orthostatic syncope.

Box 41.4. • Classification of Amyloidoses

Primary amyloidosis (AL amyloidosis)—accounts for 90% of amyloidosis in the United States

Secondary amyloidosis (AA amyloidosis)—caused by chronic infections (eg, osteomyelitis) or autoimmune disease

Familial amyloidosis—associated with mutations in transthyretin or other proteins

Senile amyloidosis—associated with aging

Localized amyloidosis—involves the skin, bladder, or other organs

Hemodialysis-associated amyloidosis—characterized by deposits of β_2-microglobulin

For AL amyloidosis, treatment with bortezomib, melphalan, and dexamethasone or cyclophosphamide, bortezomib, and dexamethasone (CyBorD) is effective. Autologous stem cell transplant provides benefit in carefully selected patients. The median survival is variable and depends on organ involvement.

Treatment of AA amyloidosis (secondary amyloidosis) involves correcting the underlying disease. Liver transplant may be valuable in familial cases in which an amyloidogenic protein is made by the liver.

Acute Leukemias

Acute leukemia is defined by the presence of at least 20% blast cells in the bone marrow. If the cells exhibit myeloid differentiation, the diagnosis is **AML**; if the cells have lymphoid markers, the diagnosis is **ALL**.

Key Definitions

Acute leukemia: *presence of ≥20% blast cells in the bone marrow.*

Acute myeloid leukemia: *acute leukemia with myeloid differentiation.*

Acute lymphocytic leukemia: *acute leukemia with lymphoid markers.*

Acute Myeloid Leukemia

The cause of AML is unknown in most cases, but there are many associations: previous myeloproliferative neoplasm or MDS; exposure to radiation or benzene; prior chemotherapy; and congenital disorders such as Down syndrome, Fanconi syndrome, and ataxia-telangiectasia.

The median age of patients with AML (Figure 41.6) is about 65 years. Patients may have nonspecific symptoms, such as fatigue and headache, or cytopenias.

For patients who have extreme leukocytosis (leukocyte count $>80\times10^9$/L) and acute leukemia at initial evaluation, the initial complication of most concern is cerebral hemorrhage due to leukostasis. Emergency treatment includes leukapheresis followed by treatment of the specific type of leukemia. Patients with acute promyelocytic leukemia (AML-M3) (Figure 41.7) typically have a t(15;17) translocation and often have disseminated intravascular coagulation.

Treatment of AML is divided into 1) induction therapy (cytarabine and an anthracycline agent) and 2) consolidation therapy (high-dose cytarabine). Relapse occurs eventually in most patients with AML. In patients with relapsed AML, reinduction of remission is followed by hematopoietic stem cell transplant. The 5-year survival rate for younger patients with a good cytogenetic profile is 60%, but for patients who have a poor cytogenetic profile or who are older, the 5-year survival rate is less than 10%.

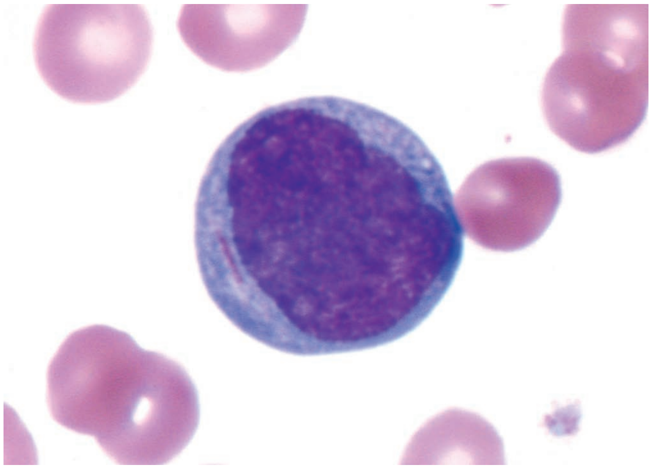

Figure 41.6. *Acute Myeloid Leukemia.*
Blast cells are large and have an open, granular nuclear chromatin, often with 1 or more nucleoli. The presence of an Auer body means that the blast is myeloid rather than lymphoid (bone marrow aspirate smear; Wright-Giemsa).

All-*trans*retinoic acid (ATRA) is the treatment of choice in AML-M3 with the t(15;17) translocation. Induction chemotherapy is with ATRA and an anthracycline-based program, followed by consolidation therapy. Maintenance therapy includes ATRA for 1 to 2 years.

Acute Lymphocytic Leukemia

ALL is most common in children; their complete remission rates are greater than 90%. In adults, however, ALL is less common and outcomes are much poorer. Remission rates in adults are up to 75%, but relapse occurs in most patients.

Bone pain, lymphadenopathy, splenomegaly, and hepatomegaly are more common in ALL than in AML.

All patients receive intensive chemotherapy with intrathecal therapy because of the risk of relapse in the central nervous system. Allogeneic stem cell transplant is recommended for patients with adverse risk factors.

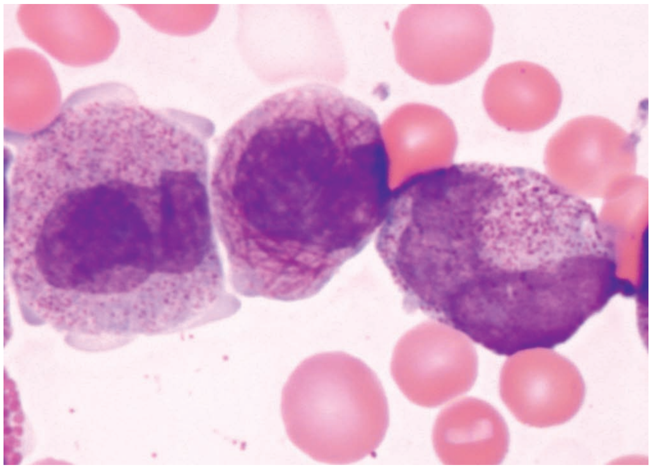

Figure 41.7. *Leukemic Cells in Acute Promyelocytic Leukemia (AML-M3).*
Abundant cytoplasmic granules and Auer bodies are present (bone marrow aspirate smear; Wright-Giemsa).
(Courtesy of Curtis A. Hanson, MD, Mayo Clinic, Rochester, Minnesota; used with permission.)

KEY FACTS

- ✓ Waldenström macroglobulinemia—
  - immunoglobulin M paraprotein
  - clonal lymphoplasmacytic cells in bone marrow
  - anemia, hyperviscosity, lymphadenopathy, or hepatosplenomegaly
- ✓ AL amyloidosis—
  - fatigue, weight loss, macroglossia
  - hepatomegaly
  - renal insufficiency, nephrotic syndrome
  - congestive heart failure, orthostatic hypotension
  - carpal tunnel syndrome, peripheral neuropathy
- ✓ AL amyloidosis with cardiac involvement—
  - electrocardiogram: low voltage or Q waves
  - echocardiogram (abnormal in 60%): concentrically thickened ventricles or thickened interventricular septum and sometimes a speckled appearance
- ✓ Acute leukemia with extreme leukocytosis—cerebral hemorrhage may result from leukostasis (treat with leukapheresis and treat specific leukemia)
- ✓ AML-M3—
  - usually t(15;17) (treat with ATRA)
  - often disseminated intravascular coagulation

Chronic Myeloid Disorders

Chronic myeloid disorders include MDS, CML, and myeloproliferative neoplasms. Patients with these disorders, in contrast to AML, have less than 20% blast cells in the bone marrow. Chronic myeloid disorders can, however, evolve into AML.

Myelodysplastic Syndromes

MDSs are heterogeneous and share 3 common features: peripheral blood cytopenia, abnormal "dysplastic" bone marrow

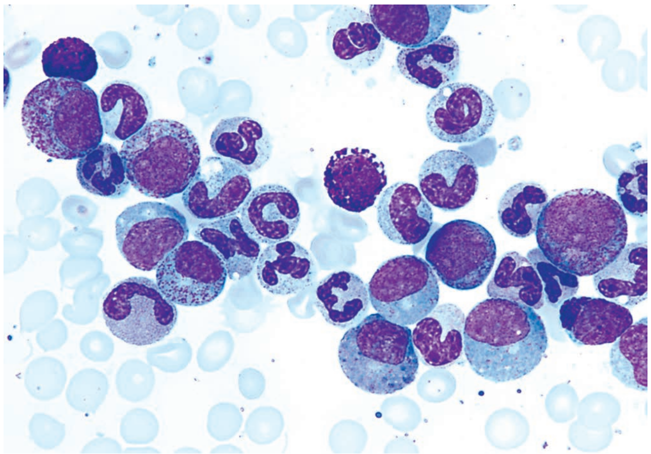

Figure 41.8. *Chronic Myeloid Leukemia.*
Normal-appearing myeloid cells show all stages of maturation, with a decreased number of erythropoietic cells and 1 basophil precursor in the center (bone marrow aspirate smear; Wright-Giemsa).
(Courtesy of Curtis A. Hanson, MD, Mayo Clinic, Rochester, Minnesota; used with permission.)

morphology, and a tendency to evolve to AML. Transformation to acute leukemia occurs in about 25% to 30% of patients. Clonal karyotypic abnormalities are common. Infection is the most common cause of death, followed by complications of AML progression and hemorrhage.

Patients with del(5q) MDS have a favorable prognosis and respond well to lenalidomide treatment. Hypomethylating agents (azacitidine or decitabine) are therapy options for those with intermediate-risk disease. Some patients may receive supportive care alone. Those who are eligible should be considered for allogeneic bone marrow transplant.

Chronic Myeloid Leukemia

CML constitutes 20% of all leukemias. The Philadelphia chromosome, t(9;22), is the hallmark of this disease. The molecular equivalent of the Philadelphia chromosome is the abnormal BCR-ABL fusion protein (Figure 41.8).

Symptoms include malaise, dyspnea, anorexia, fever, night sweats, weight loss, abdominal fullness, gout, and priapism. Splenomegaly is present in 85% of patients.

Characteristic laboratory findings include leukocytosis. Leukocyte counts of 100×10^9/L are common, but leukapheresis is not usually required because the leukocytes are mature and do not cause leukostasis. Granulocytes in all stages of maturation are present in peripheral blood smears, with basophilia and eosinophilia and a characteristic *myelocyte bulge* (ie, increased numbers of myelocytes in relation to other stages of granulocyte differentiation).

Standard treatment is a tyrosine kinase inhibitor, such as imatinib, which inhibits the BCR-ABL fusion protein. Patients who are resistant to tyrosine kinase inhibitors may be eligible for allogeneic stem cell transplant.

Philadelphia Chromosome–Negative Myeloproliferative Neoplasms

The classic myeloproliferative neoplasms include polycythemia vera, primary myelofibrosis, and essential thrombocythemia. Their characteristic features are listed in Table 41.5. These disorders may progress to AML, which is usually refractory to therapy. Each of these disorders carries a risk of thrombosis and hemorrhage.

Activating mutations involving JAK2 tyrosine kinase are present in almost all patients with polycythemia vera and in about half of those with primary myelofibrosis or essential thrombocythemia.

Primary Myelofibrosis, Postpolycythemic Myelofibrosis, and Postthrombocythemic Myelofibrosis

Splenomegaly occurs in virtually all patients with myelofibrosis and is a hallmark of primary myelofibrosis. Other features are a leukoerythroblastic peripheral blood smear, including nucleated red blood cells and dacryocytes (teardrop cells), and hypercellular marrow with increased fibrosis (Figure 41.9).

Foci of extramedullary hematopoiesis can occur in any area of the body but are most common in the spleen, liver, lung and pleural space, skin, eye, and central nervous system. The median survival is 3 to 5 years.

Table 41.5 • Characteristic Features of Chronic Myeloproliferative Disorders

Characteristic	Polycythemia Vera	Primary Myelofibrosis	Essential Thrombocythemia	Chronic Myeloid Leukemia
Increased erythrocyte mass	Yes	No	No	No
Myelofibrosis	Later	Yes	Rare	Later
Leukocytosis	Variable	Variable	Variable	Yes
Thrombocytosis	Variable	Variable	Yes	Variable
BCR-ABL oncogene	No	No	No	Yes
JAK2 V617F mutation	>95%	50%	50%	Never

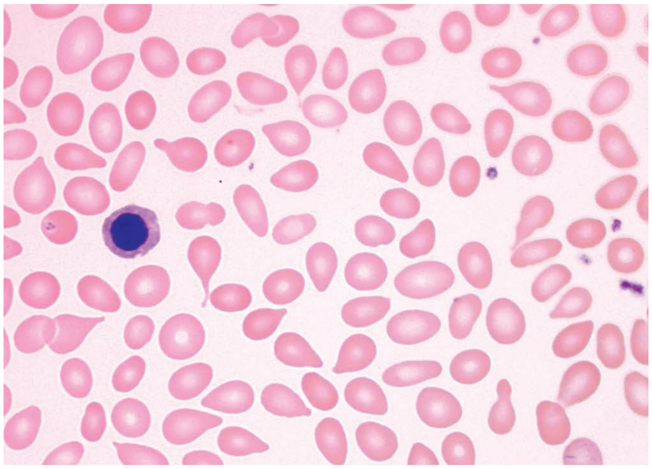

Figure 41.9. *Leukoerythroblastic Blood Smear.*
The teardrop-shaped erythrocytes (dacryocytes) and nucleated red blood cell are characteristic of marrow fibrosis, whether due to primary myelofibrosis or a reactive cause (peripheral blood smear; Wright-Giemsa).

Asymptomatic patients should be observed. Medical therapy for anemia includes transfusion with packed red blood cells, androgens, or erythropoietin. Some patients respond to thalidomide or lenalidomide.

Essential Thrombocythemia

Essential thrombocythemia is a clonal hematologic disorder that presents with thrombocytosis and sometimes leukocytosis. Patients may be asymptomatic, or they may have thrombosis or hemorrhage. Most patients have a normal life expectancy. The risk of acute leukemic transformation is less than 5% at 15 years.

Diagnostic features of essential thrombocythemia include a sustained platelet count greater than 450×10^9/L, megakaryocytic hyperplasia in the bone marrow, and absence of the Philadelphia chromosome. It may be challenging to distinguish essential thrombocythemia from reactive thrombocytosis or iron deficiency.

Treatment depends on the clinical situation. All patients who can tolerate aspirin should receive low-dose aspirin. Platelet apheresis should be used only for emergent management of acute bleeding or thrombosis and is not indicated on the basis of the platelet count alone. Cytoreductive therapy is recommended for patients with acute thrombosis or a previous history of thrombosis and for patients older than 60 years. Young asymptomatic patients may be observed.

Polycythemia Vera

Polycythemia vera is a myeloproliferative disorder that results from activating mutations involving JAK2 tyrosine kinase. Clinical features include postbathing pruritus, fatigue, erythromelalgia, and headache. More than 50% of patients have leukocytosis and thrombocytosis in addition to erythrocytosis. Polycythemia vera should be considered in the evaluation of an idiopathic thrombosis, especially in an atypical site such as an abdominal vessel or a dural sinus in the brain.

Bone marrow findings in polycythemia vera typically include trilineage hyperplasia. Erythropoietin levels are low or low normal.

The mainstay of therapy for all patients with polycythemia vera is phlebotomy, with the goal of maintaining the hematocrit at less than 45%. Low-dose aspirin therapy is indicated for all patients who do not have a contraindication. For patients who are older than 60 years or who have had prior thrombosis, cytoreductive therapy is indicated.

KEY FACTS

✓ CML—

- 20% of all leukemias
- hallmark: Philadelphia chromosome, t(9;22)
- treatment: tyrosine kinase inhibitor (eg, imatinib), which inhibits BCR-ABL fusion protein

✓ Activating mutations involving JAK2 tyrosine kinase—

- in nearly 100% of patients with polycythemia vera
- in 50% of patients with primary myelofibrosis or essential thrombocythemia

✓ Polycythemia vera—a consideration in idiopathic thrombosis, especially in atypical site (eg, abdominal vessel or dural sinus in brain)

42

Thrombotic Disorders

RAJIV K. PRUTHI, MBBS

Thrombophilia: The Hypercoagulable States

Thrombophilia refers to the tendency for thromboembolism (ie, having risk factors for thromboembolism), which may be inherited or acquired (Box 42.1). As the number of risk factors increases, the risk of venous thromboembolism (VTE) also increases. Antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, and anti–β_2-glycoprotein I antibodies) and hyperhomocysteinemia are risk factors not only for VTE but also for arterial thrombosis.

Key Definition

Thrombophilia: *tendency for thromboembolism (ie, having inherited or acquired risk factors for thromboembolism).*

VTE (which comprises deep vein thrombosis [DVT] and pulmonary embolism [PE]) affects 1 in 1,000 people; this increases to 1 in 100 among those older than 70 years in the western hemisphere. VTE is a major cause of morbidity, and the annual mortality rate of 50,000 is higher than that for breast cancer.

PE is the cause of death in 5% to 15% of hospitalized patients. Factors for poor prognosis include age older than 70 years, cancer, congestive heart failure, chronic obstructive pulmonary disease, systolic arterial hypotension, tachypnea, and right ventricular hypokinesis. PE is detected in 25% to 30% of routine autopsies. Antemortem diagnosis is made in less than 30%, owing to the variable and nonspecific presentation of PE.

The most common cause of PE is DVT of the lower extremities. In approximately 45% of patients with femoral and iliac DVT, emboli move to the lungs. Other sources of emboli include thrombi in the upper extremities, right ventricle, and indwelling catheters. The congenital and acquired risk factors for PE are listed in Box 42.1. The incidence of DVT in various clinical circumstances is listed in Table 42.1.

Thrombophilic defects can be broadly classified into abnormalities of the procoagulant system and abnormalities of the anticoagulant system.

Defects in the Procoagulant System

Inherited Risk Factors for VTE

Factor V Leiden

The most common inherited defect is activated protein C (APC) resistance due to the factor V Leiden (FVL) mutation (R506Q). This causes activated factor V to be resistant to inactivation by APC. The condition is common among white people but rare among people of Asian or African ancestry.

Laboratory testing consists of performing the APC resistance assay and, if the results are abnormal, follow-up DNA-based testing for FVL to determine whether the person is heterozygous or homozygous (Box 42.2).

Prothrombin G20210A

The second most common defect is the prothrombin G20210A mutation, which results in an increased plasma prothrombin level. The heterozygous mutation has a prevalence of approximately 3% in the healthy white population and 6% to 18% among persons with VTE. Heterozygotes have an approximately 2-fold increased risk of VTE. These defects are common among white people and rare among people of Asian or

Box 42.1 • Inherited and Acquired Thrombophilia

- Inherited thrombophilia
    - Activated protein C resistance due to factor V Leiden mutation
    - Prothrombin G20210A mutation
    - Anticoagulant deficiencies: antithrombin, protein C, protein S
    - Selected dysfibrinogenemia
- Acquired thrombophilia
    - Lupus anticoagulant or antiphospholipid antibody syndrome
    - Pregnancy
    - Immobilization (trauma, postoperative state)
    - Estrogens (oral contraceptives, hormone replacement therapy)
    - Solid organ cancer
    - Myeloproliferative diseases
    - Paroxysmal nocturnal hemoglobinuria
    - Prolonged travel
    - Obesity
    - Age
- Mixed risk factors
    - Hyperhomocysteinemia
    - Increased levels of factors VIII, IX, and XI

African ancestry. Laboratory testing consists of DNA-based testing for the presence or absence of the mutation.

Other Risk Factors for VTE

Additional abnormalities of procoagulant proteins that confer an increased risk of VTE include increased levels of factors VIII, IX, and XI. Currently, there is no established cutoff for this increased risk and there is no known genetic basis for these abnormalities. Although abnormalities of fibrinogen (dysfibrinogenemias) generally pose a bleeding risk, rare variants pose a risk of venous or arterial thrombosis rather than hemorrhage.

Defects in the Anticoagulant System

Congenital deficiencies of the anticoagulants antithrombin, protein C, and protein S confer an increased risk of VTE. In most patients, VTE develops by age 50 years.

Acquired Risk Factors for VTE

Patients with antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, and anti–β_2-glycoprotein I antibodies) have a serious risk of both venous thrombosis and arterial thrombosis. Antiphospholipid antibody syndrome is characterized by clinical and laboratory criteria that include 1) vascular thrombosis (venous or arterial) or recurrent miscarriage, or both, and 2) the presence and persistence (on subsequent testing after 12 weeks) of lupus anticoagulant or medium to high titers of anticardiolipin or anti–β_2-glycoprotein I antibody.

If testing of asymptomatic patients shows the presence of antiphospholipid antibodies, empirical anticoagulant therapy is not recommended. However, such patients should receive VTE prophylaxis in the appropriate high-risk clinical situations. Patients with vascular thrombosis and persistent antiphospholipid antibodies should be treated with long-term therapeutic anticoagulation, and women with recurrent fetal loss benefit from heparin (unfractionated heparin [UFH] or low-molecular-weight heparin [LMWH]) in combination with aspirin during pregnancy to prevent recurrent fetal loss.

Other acquired risk factors for VTE include immobilization (eg, hospitalization or paralysis), orthopedic or general surgery, cancer and chemotherapy, and estrogen-containing drugs, which pose a considerable risk of VTE. When any of these risk factors is combined with an underlying inherited risk factor (eg, FVL), the chances of symptomatic VTE increase significantly.

Table 42.1 • VTE Risk Factors and Incidence

			Incidence, %			
Level of Risk	**Surgery**	**Additional Risk Factors**	**CVT**	**Proximal DVT**	**Clinical PE**	**Fatal PE**
Low	Minor	None	2	0.4	0.2	0.002
Moderate	Minor	Yes	10-20	2-4	1-2	0.1-0.4
High	Major	Yes	20-40	4-8	2-4	0.4-1.0
Very high	Major (hip or knee arthroplasty, hip fracture, major trauma, spinal cord injury)	Prior VTE, active cancer	40-80	10-20	4-10	0.2-0.5

Abbreviations: CVT, calf vein thrombosis; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Box 42.2 • FVL Mutation Prevalence and Risk of VTE

Prevalence of heterozygous mutation
  In the healthy white population, 5%-7%
  Among persons with VTE, 20%-50%
Risk of VTE
  For heterozygotes, relative risk is increased 2- to 4-fold (absolute annual risk is about 0.45%)
  For homozygotes, relative risk is increased 80-fold
  Compared with oral contraceptive users without FVL, FVL carriers taking estrogen-containing oral contraceptives have a relative risk of VTE that is increased up to 30-fold (absolute annual risk is about 0.3%)

Abbreviations: FVL, factor V Leiden; VTE, venous thromboembolism.

Mixed Inherited and Acquired Risk Factors for VTE

Hyperhomocysteinemia is a risk factor for VTE; certain genetic determinants (eg, *MTHFR* gene mutations) may predispose persons to hyperhomocysteinemia when compounded by acquired determinants (eg, dietary deficiencies of folate and vitamins B_6 and B_{12}). However, in the absence of hyperhomocysteinemia, routine testing for the *MTHFR* gene mutation is not indicated.

VTE as a Multifactorial Condition

Patients with inherited risk factors have a baseline increased risk. Symptomatic VTE develops when inherited risk factors are present in combination with acquired risk factors, such as pregnancy, estrogen use, or surgery.

Prevention of VTE

All hospitalized medical, surgical, and trauma patients should be assessed for the risk of VTE and given appropriate VTE prophylaxis (Box 42.3). The risk of VTE must be balanced against the risk of hemorrhage and the presence of contraindications to anticoagulation (Table 42.1). The risk of VTE in surgical patients varies with the site of surgery, surgical technique, duration of the procedure, type of anesthesia, complications (eg, infection or shock), and degree of immobilization. High-risk surgical procedures include open abdominal or urologic surgery, neurosurgery, gynecologic surgery, and orthopedic surgery of the lower extremities (joint replacement and hip fracture repair). In addition, patient-related risk factors include intensive care unit admission, older age, cardiac dysfunction, acute myocardial infarction, congestive heart failure, cancer and its treatment, paralysis, prolonged immobility, prior VTE, obesity, varicose veins, central venous catheters, inflammatory bowel disease, lobar pneumonia, nephrotic syndrome, pregnancy, and estrogen use.

KEY FACTS

✓ Antiphospholipid antibodies and hyperhomocysteinemia—risk factors for both VTE and arterial thrombosis

✓ Relative risk of VTE for oral contraceptive users—up to 30-fold higher for FVL carriers (vs users without FVL)

✓ Relative risk of VTE for FVL homozygotes—80-fold higher

✓ VTE prevention—assess VTE risk for all hospitalized medical, surgical, and trauma patients and give appropriate prophylaxis

Evaluation for VTE

Among ambulatory patients who have symptoms worrisome for VTE, more than 75% are found not to have VTE on radiologic testing. Thus, a sensitive and specific strategy to decrease excess radiologic imaging studies without compromising patient safety is required. A history should be obtained to assess for the presence of acquired risk factors for VTE. Considerations in the clinical evaluation include patient and family history of VTE, pregnancy, recurrent miscarriage, estrogen use, recent trauma, surgery, hospitalization, cancer, and travel. A physical examination should include evaluation for venous stasis and an

Box 42.3 • Suggested Strategies for VTE Prophylaxis

1. Education and early ambulation—Educate all patients about the signs and symptoms of VTE and the role of prophylaxis. Encourage patients to walk as early and as often as feasible.
2. Low-risk patients—Focus on education and early ambulation.
3. Moderate- or high-risk patients—Same as for low-risk patients, with the additions of elastic graded compression stockings (below knee), intermittent pneumatic compression if immobilized, and pharmacologic prophylaxis (UFH and LMWH are equivalent).
4. Very high-risk patients—Same as for moderate- or high-risk patients but with the following differences: UFH is not recommended; LMWH, fondaparinux, and adjusted-dose warfarin are used to keep the INR between 2.0 and 3.0; and extended out-of-hospital prophylaxis may be needed.
5. Patients with a previous history of VTE or thrombophilia—Same strategies as for very high-risk patients.

Abbreviations: INR, international normalized ratio; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism.

underlying malignant process. The most critical initial component of the examination is to confirm or rule out venous limb gangrene (ie, **phlegmasia cerulea dolens**), in which severe obstruction of extremity venous drainage leads to congestion and eventual obstruction of arterial inflow. If venous limb gangrene is present, thrombolytic therapy, fasciotomy, or thrombectomy may be indicated.

Key Definition

Phlegmasia cerulea dolens: *venous limb gangrene from severe obstruction of venous drainage in the extremity, leading to congestion and eventual obstruction of arterial inflow.*

Clinical findings alone, although important, are poor predictors of the presence or severity of VTE, and objective diagnostic testing may eventually be required. Initial steps, however, consist of estimating the clinical pretest probability of VTE and using the D-dimer assay, with further diagnostic testing as indicated.

Step 1: Determining the Clinical Pretest Probability

The Wells model (Table 42.2) categorizes the pretest probability of DVT as high (≥3 points), moderate (1 or 2 points), or low (<1 point). A similar model applied to PE (Table 42.3) stratifies patients according to whether PE is less likely (≤4) or more likely (>4). For patients in the low-risk category, determining the level of D-dimer (a breakdown product from cross-linked stabilized fibrin clots) is recommended. The result helps to determine whether further imaging studies are needed.

Table 42.2 • Wells Model for Predicting Clinical Pretest Probability of Deep Vein Thrombosis

Clinical Variable	Points[a]
Active cancer	1
Paralysis or recent limb casting	1
Recent immobility for >3 d	1
Local vein tenderness	1
Limb swelling	1
Unilateral calf swelling >3 cm	1
Pitting edema	1
Collateral superficial vein	1
Alternative diagnoses likely	−2

[a] Pretest probability of deep vein thrombosis according to total score: ≥3 points, high; 1 or 2 points, moderate; <1 point, low.

Table 42.3 • Wells Model for Predicting Clinical Pretest Probability of Pulmonary Embolism

Clinical Variable	Points[a]
Clinical signs and symptoms of DVT	3
Alternative diagnoses less likely	3
Heart rate >100 beats per minute	1.5
Immobilization or surgery in previous 4 wk	1.5
Previous DVT or pulmonary embolism	1.5
Hemoptysis	1
Cancer	1

Abbreviation: DVT, deep vein thrombosis.

[a] Pretest probability of pulmonary embolism according to total score: ≤4 points, less likely; >4 points, more likely.

Step 2: Determining the D-Dimer Level

For ambulatory outpatients, a D-dimer level within the reference range has a high negative predictive value for DVT; thus, additional imaging tests to exclude VTE are unnecessary. High levels have a low positive predictive value for PE so should be used only in conjunction with the clinical pretest probability assessment. (Advanced age and pregnancy are associated with increased levels.) Recent data suggest that using age-adjusted D-dimer levels (age×10 mcg/L), for highly sensitive D-dimer assays, would further decrease the number of imaging studies that are currently performed. The D-dimer test should be used only for ambulatory outpatients. It should not be used to exclude VTE in hospitalized patients; in patients with cancer or recent trauma, surgery, or hemorrhage; or in patients with an intermediate or high clinical probability of VTE. It is appropriate for these patients to proceed directly to imaging studies.

Diagnostic Approach for DVT

For patients with a low clinical pretest probability and normal D-dimer results, DVT is effectively ruled out and no radiologic imaging is needed unless new or progressive symptoms occur. With this approach, VTE subsequently develops in less than 1% of patients.

For patients with a moderate or high clinical pretest probability, diagnostic imaging studies should be performed (eg, duplex ultrasonography with compression). If the imaging study results are negative, checking the D-dimer level is reasonable. If the level is increased, further imaging studies are indicated.

Compression ultrasonography, the most commonly used noninvasive test, has a diagnostic accuracy of 90% to 95% in detecting iliac and femoral DVT. Serial compression ultrasonography is recommended for high-risk patients because it has a 15% detection rate for DVT after an initial negative study. Magnetic resonance imaging has a high sensitivity and specificity for the diagnosis of pelvic DVT.

Diagnostic Approach for PE

PE should be considered in patients with dyspnea, pleuritic chest pain, and tachypnea. Hemodynamic stability should be assessed. Alternative therapies such as thrombolytic therapy or surgical thrombectomy may be indicated. Results of physical examination, electrocardiography, chest radiography, blood gas assessment, and measurement of troponin, B-type natriuretic peptide (BNP), and plasma D-dimer levels have low specificity and sensitivity for the diagnosis of PE, but when considered together, they may be helpful.

BNP and NT-proBNP (the N-terminal fragment of the BNP precursor) are specific markers of ventricular stress and have a strong correlation with right ventricular dysfunction in patients with PE. Patients who have PE and high levels of BNP are at higher risk for in-hospital adverse events (odds ratio, 6.8) and 30-day all-cause death (odds ratio, 7.6). Chest radiographic findings may be normal and electrocardiographic findings nonspecific.

Both the Pao_2 (arterial partial pressure of oxygen) and the PAo_2–Pao_2 (alveolar-arterial gradient in the partial pressure of oxygen) may be normal in 15% to 20% of patients. The PAo_2–Pao_2 shows a linear correlation with the severity of PE, but a normal PAo_2–Pao_2 does not exclude PE. Most patients with acute PE are hypocapnic.

Ventilation-perfusion scanning is used less commonly in the diagnosis of acute PE and is generally reserved for patients with renal insufficiency or allergy to contrast agents. A "high-probability" ventilation-perfusion lung scan has a sensitivity of 41% and a specificity of 97% (90% probability of PE). A "low-probability" lung scan excludes the diagnosis of PE in more than 85% of patients. An "intermediate-probability" lung scan is associated with PE in 21% to 30%. Therefore, an intermediate-probability lung scan usually requires additional study. A negative or normal perfusion-only scan (excluding a ventilation scan) rules out PE with a very high probability.

Computed tomography (CT) angiography permits ultrafast scanning of pulmonary arteries during contrast injection. Sensitivity and specificity rates greater than 95% have been reported. Spiral CT has the greatest sensitivity in the diagnosis of PE in the main, lobar, or segmental arteries. Because of the distal nature of the thrombotic material in chronic thromboembolic disease, ventilation-perfusion scanning is preferred in these patients. Magnetic resonance imaging may have the advantage of detecting both DVT and PE. Dysfunction of the right ventricle (frequently seen in submassive, massive, and recurrent PE) can be detected with transthoracic Doppler echocardiography. Echocardiography is not necessary for all patients with PE, especially those with normal BNP levels; however, it is extremely useful for patients who are clinically unstable.

Pulmonary angiography is the diagnostic standard but has been largely replaced by CT angiography. It should be performed within 24 to 48 hours after the diagnosis has been considered. After pulmonary angiography, major complications occur in 1% of patients, and minor complications in 2%; the mortality rate from the procedure is 0.5%.

Patients with PE should be hospitalized for at least 24 hours to assess clinical stability. Select asymptomatic, clinically stable patients may be treated as outpatients with LMWH and warfarin as described above.

Thrombophilia Testing

For patients who have VTE after a temporary risk factor (eg, recent surgery, immobilization, or pregnancy) and do not have a family history of VTE, thrombophilia testing is not recommended. In other subgroups of patients, it is reasonable to consider thrombophilia testing, with the recognition that certain assays are affected by acute thrombotic events, heparin, and warfarin. Testing should be considered if results will affect long-term management of anticoagulation. Thrombophilia testing can be performed before initiation of anticoagulation or after completion of anticoagulation appropriate for a thrombotic event if certain caveats are recognized and appropriate follow-up testing is performed.

DNA-based testing (eg, FVL and prothrombin G20210A mutation) is not affected by acute thrombosis, heparin anticoagulation, or warfarin. However, the optimal time for thrombophilia testing is 4 to 6 weeks after completion of anticoagulation.

Thrombophilia does not alter acute management of VTE except in certain circumstances. If the baseline activated partial thromboplastin time (aPTT) is prolonged in association with lupus anticoagulants, it is reasonable to consider monitoring of the UFH complex, use of the heparin assay (anti-Xa levels), or use of LMWH (which requires no monitoring). With congenital deficiency of protein C or protein S, the risk of warfarin skin necrosis increases, especially if heparin therapy (with UFH or LMWH) is prematurely discontinued (see Treatment of VTE section). For thrombophilic conditions that impart a high risk of recurrence, a longer duration of anticoagulation is needed.

Idiopathic DVT, particularly when recurrent, may indicate the presence of neoplasm in 10% to 20% of patients.

For patients with objectively confirmed VTE, initial laboratory testing should include a complete blood cell count (and, if abnormal, a blood smear), serum tests of liver and kidney function, measurement of baseline prothrombin time and aPTT (before initiation of anticoagulant therapy), and urinalysis. Testing should also include age-appropriate cancer screening. Additional testing (eg, radiologic studies) should be reserved for further investigation of abnormal initial history, examination, and laboratory findings and patient risk factors (eg, smoking).

KEY FACTS

- ✓ VTE evaluation—
  - first, determine clinical pretest probability
  - second, determine D-dimer level
- ✓ D-dimer test to exclude VTE—
  - use for ambulatory outpatients only
  - do not use in patients who are hospitalized; who have cancer or recent trauma, surgery, or hemorrhage; or who have intermediate or high clinical probability of VTE
- ✓ Serial compression ultrasonography for DVT diagnosis—recommended for high-risk patients (15% DVT detection rate after initial negative study)
- ✓ Thrombophilia testing—
  - not recommended if patient has a temporary risk factor (eg, recent surgery, immobilization, or pregnancy) and does not have a family history of VTE
  - consider performing if results would affect long-term management of anticoagulation

Treatment of VTE

Initial Management of VTE

The aims of initial therapy for VTE include preventing extension or embolization of the thrombus and reducing postphlebitic syndrome. Patients who are hemodynamically unstable should be hospitalized. For most hemodynamically stable patients, however, outpatient anticoagulation is reasonable. After contraindications to anticoagulation have been excluded, several options for acute and long-term anticoagulation are available, depending on the oral anticoagulant agent chosen.

For patients who will be treated with warfarin, therapeutic doses of either intravenous UFH or subcutaneous LMWH, along with simultaneous oral warfarin therapy, should be started. UFH is monitored with aPTT or heparin levels (anti-Xa assay); LMWH does not need monitoring, but the international normalized ratio (INR) is used to assess warfarin effect. Therapy with both agents should be continued for at least 5 days or until the INR is in the therapeutic range (ie, 2-3) for at least 48 hours before discontinuing the UFH or LMWH.

For patients who will be treated with oral direct-acting anticoagulants—such as direct thrombin inhibitors (eg, dabigatran) or edoxaban (an oral direct factor Xa inhibitor)—therapy should be transitioned to the oral agent *after* a period of initial treatment with UFH or LMWH. For patients who will be treated with oral direct factor Xa inhibitors rivaroxaban or apixaban, initial UFH or LMWH is not required.

Use of knee-high compression stockings has been shown to decrease the incidence of postphlebitic syndrome.

Calf Vein Thrombosis

Patients with asymptomatic calf vein thrombosis can be observed if they are willing and able to return for follow-up compression ultrasonography to document stability or progression of the clot. If patients have symptomatic or progressive calf vein thrombosis, anticoagulation should be initiated.

Proximal DVT

Management of proximal DVT should be as described above in the Initial Management of VTE section.

Pulmonary Embolism

Thrombolytic Therapy

For patients with massive PE or PE with hemodynamic instability, thrombolytic therapy is recommended. The use of thrombolytics in submassive, hemodynamically stable PE is controversial. Ideally, thrombolytic agents should be administered within 24 hours after PE presentation. After thrombolytic therapy, heparin infusion is begun or resumed if the aPTT is less than 80 seconds. The risk of intracranial bleeding in patients who have PE treated with thrombolytic drugs is about 1%.

Inferior Vena Cava Interruption

Inferior vena cava interruption is indicated if anticoagulant therapy is contraindicated, if complications result from anticoagulant therapy, if anticoagulant therapy fails, if a predisposition to bleeding is present, if chronic recurrent PE and secondary pulmonary hypertension occur, or if surgical pulmonary thromboendarterectomy has been performed or is intended to be performed. After the filter has been inserted, anticoagulant therapy is aimed at preventing DVT at the insertion site, inferior vena cava thrombosis, cephalad propagation of a clot from an occluded filter, and propagation or recurrence of lower extremity DVT. PE occurs in 2.5% of patients despite inferior vena cava interruption.

Long-Term Management of VTE (Secondary Prophylaxis)

The aim of long-term therapy for VTE is secondary prevention or decreasing the risk of recurrence. After an initial 3 months

Table 42.4 • Duration of Anticoagulation for Long-term Management of VTE

Clinical Situation	Duration of Anticoagulation
VTE from temporary risk factor (eg, surgery or pregnancy)	Discontinue anticoagulation at 3 mo
VTE from persistent risk factor	Continue oral agent (warfarin or direct-acting anticoagulants) for extended duration
DVT without risk factors (idiopathic)	Additional 3 mo of warfarin for secondary prophylaxis
Recurrent DVT	Extended secondary prophylaxis
PE—hemodynamically significant or idiopathic	Long-term treatment with warfarin
VTE with underlying thrombophilia (eg, from lupus anticoagulant or deficiency of protein C, protein S, or antithrombin)	Long-term treatment with warfarin
VTE in patients who are compound heterozygous for factor V Leiden and prothrombin G20210A mutation	Long-term treatment with warfarin

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

of anticoagulation, a decision should be made on the duration of anticoagulation (Table 42.4). A decision to continue warfarin anticoagulation should be balanced against the risk of hemorrhage. For patients receiving warfarin, the INR is monitored every 4 to 6 weeks. For patients receiving a direct-acting anticoagulant, monitoring is not needed. Long-term outcomes are superior when VTE is managed in anticoagulation clinics and with home INR measuring devices.

KEY FACTS

✓ Initial management of VTE—

- if oral direct-acting anticoagulants (eg, direct thrombin inhibitors) or the oral direct factor Xa inhibitor edoxaban will be used, transition to these drugs after use of UFH or LMWH
- if oral direct factor Xa inhibitors rivaroxaban or apixaban will be used, initial use of UFH or LMWH is not necessary

✓ Thrombolytic therapy—recommended for patients with massive PE or PE with hemodynamic instability

✓ Indications for inferior vena cava interruption—

- anticoagulant therapy is contraindicated, results in complications, or fails
- patient has predisposition to bleeding or has chronic recurrent PE and secondary pulmonary hypertension
- surgical pulmonary thromboendarterectomy has been or will be performed

✓ Long-term management of VTE—

- discontinue anticoagulation if risk factor is temporary (eg, surgery or pregnancy)
- give warfarin for 3 more months for idiopathic DVT
- provide extended secondary prophylaxis for recurrent DVT
- give long-term warfarin for hemodynamically significant or idiopathic PE, for VTE with thrombophilia, and if the patient is compound heterozygous for FVL and prothrombin G20210A mutation

VI

Questions and Answers

Questions

Multiple Choice (Choose the best answer)

VI.1. A 45-year-old woman is evaluated for fatigue and low back pain for the past 3 months. Her medical history is significant for migraines and menorrhagia. On physical examination she is pale with cracking at the sides of her lips (angular cheilitis). Results of laboratory studies are as follows: white blood cell count 5.2×10^9/L, hemoglobin 8.0 g/dL, mean corpuscular volume 67 fL, red blood cell (RBC) distribution width 16%, and platelet count 290×10^9/L. The peripheral blood smear is shown in Figure VI.Q1:

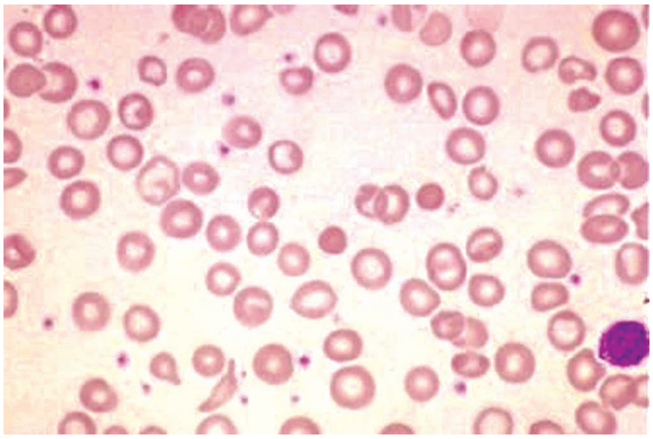

Figure VI.Q1.

What is the best next test for establishing a diagnosis?

a. Reticulocyte count
b. Serum iron, total iron-binding capacity (TIBC), and transferrin saturation
c. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
d. Serum ferritin

VI.2. A 22-year-old man with sickle cell disease has a history of frequent pain crises. His baseline hemoglobin level is 9 g/dL, and his reticulocyte count is 92 to 340×10^9/L (3%-11%). He seeks care at the emergency department with "pain all over" for the past 2 days. He has no fever or dyspnea. His hemoglobin at this time is 7.8 g/dL, and the reticulocyte count is 443×10^9/L (16%). What is the best step in management to prevent such episodes in the future?

a. Red blood cell transfusion
b. Hydroxyurea
c. Opioids
d. Intravenous hydration

VI.3. A 30-year-old healthy woman is being evaluated by her primary care provider for anemia. She reports no bleeding. She is taking no medications and reports no use of alcohol or illicit drugs. Results of laboratory studies show the following: hemoglobin 11.5 g/dL, mean corpuscular volume 68 fL, red blood cell (RBC) count 5.5×10^{12}/L, and RBC distribution width (RDW) 14%. The white blood cell count and platelet count are normal. What is the most likely diagnosis?

a. Iron deficiency anemia
b. Anemia of chronic disease
c. Thalassemia
d. Sideroblastic anemia

VI.4. An 18-year-old woman seeks care for prolonged bleeding after a wisdom tooth extraction performed 1 week ago. The socket continues to bleed and is staining her pillow at night; it temporarily stops if she applies pressure with a cotton ball. Her menarche was at age 13 years, and she has had menorrhagia such that she had to stay home from school at least 2 times per year. She has been told she is iron deficient. She has not previously undergone other invasive procedures. Her family history is significant for 1 of her maternal aunts having menorrhagia and requiring hysterectomy that was complicated by bleeding. A maternal uncle and a male cousin also have had excessive bleeding, but additional details are not available. Laboratory results of serum tests of renal and hepatic function are normal. Additional laboratory data are as follows: white blood cell count 5.5×10^9/L, hemoglobin 11.0 g/dL, mean corpuscular volume 78 fL, red blood cell distribution width 18%, platelet count 400×10^9/L, prothrombin time (international normalized ratio) 10 s (1.0), activated partial thromboplastin time (aPTT) 30 s, and microcytes on peripheral blood smear. What is the most appropriate next diagnostic test?

a. Factor VII
b. Factor VIII inhibitor
c. von Willebrand factor assays
d. Factor IX

VI.5. A 20-year-old woman is referred for evaluation of thrombocytopenia. She has no chronic illnesses, is taking no medications, and is currently in her first trimester of pregnancy. During a routine antenatal visit, a complete blood cell count (CBC) ordered by her obstetrician shows a platelet count of 60×10^9/L. She reports no personal or family history of bleeding disorders. Her physical examination is normal for the first trimester of pregnancy. What is the most appropriate next step in management?
a. Perform bone marrow aspiration and biopsy
b. Perform liver/spleen imaging to assess for splenomegaly
c. Repeat the CBC with specimen collected in citrate
d. Test for antiplatelet antibodies

VI.6. A 54-year-old woman is receiving follow-up care for thrombocytopenia. Approximately 1 year ago, she was seen by a hematologist for a platelet count of 100×10^9/L and minimal bruising. Her diagnosis was believed to be consistent with chronic autoimmune thrombocytopenia. Since then, she has had occasional bruising and minor bleeding with cuts from kitchen knives while cutting vegetables. She has no additional personal or family history of bleeding. She has no chronic illnesses and is currently taking no medications. One week ago, a bruise developed on her left thigh after she bumped into a door handle. Physical examination indicates no evidence of wet purpura on her oral mucosa, lymphadenopathy, or hepatosplenomegaly. She has a resolving bruise on her left thigh. A complete blood cell count (CBC) shows normal hemoglobin value and white blood cell count but a platelet count of 80×10^9/L. A peripheral blood smear excludes pseudothrombocytopenia. What is the most appropriate next step in management?
a. Continue to observe with periodic CBCs
b. Bone marrow aspiration biopsy
c. Computed tomography of the chest, abdomen, and pelvis
d. Platelet aggregation studies

VI.7. A 39-year-old man seeks care at the emergency department for a 1-week history of easy bruising, fatigue, shortness of breath, and fever. Findings on complete blood cell count are hemoglobin 6.9 g/dL, platelet count 13×10^9/L, and white blood cell (WBC) count 102×10^9/L. A peripheral blood smear is shown in Figure VI.Q7:

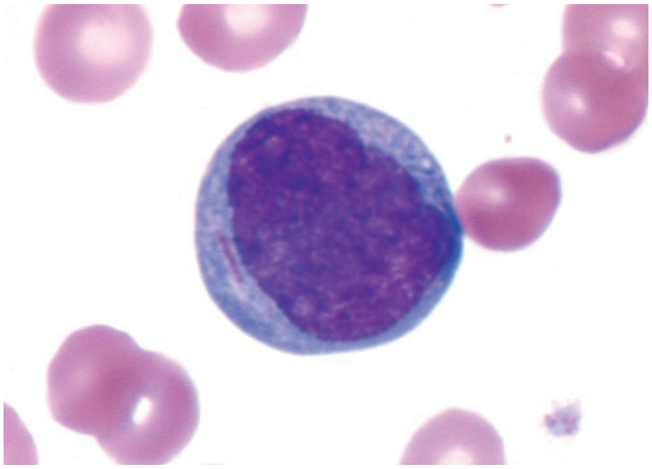

Figure VI.Q7.

What is the best next step in therapy?
a. Packed red blood cell transfusion
b. Intravenous dexamethasone, 10 mg
c. Leukapheresis
d. Plateletpheresis

VI.8. A 59-year-old woman seeks care at an outpatient clinic for decreased appetite, abdominal discomfort, and fatigue. A complete blood cell count shows a "myelocyte bulge," which indicates the need for a bone marrow biopsy. A bone marrow aspirate is shown in Figure VI.Q8:

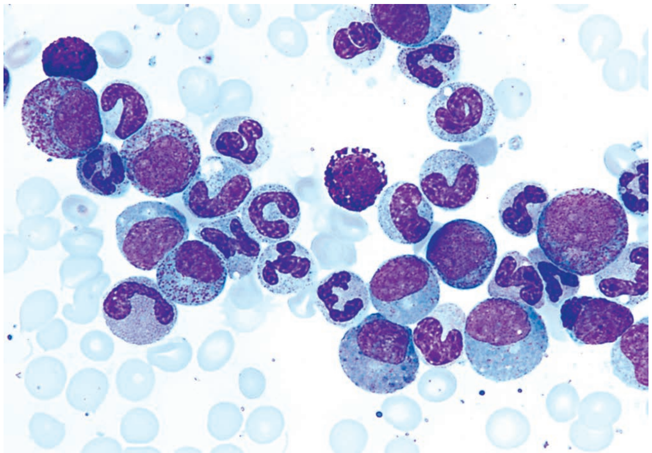

Figure VI.Q8.

What is the best next step in management?
a. Cytarabine and daunorubicin ("7+3")
b. R-CHOP
c. Lenalidomide
d. Imatinib mesylate

VI.9. A 71-year-old woman undergoes preoperative evaluation before knee replacement. She is asymptomatic with the exception of left knee pain. Her white blood cell count is 14.3×10^9/L, hemoglobin value is 14.1 g/dL, and platelet count is 381×10^9/L. A peripheral blood smear is shown in Figure VI.Q9:

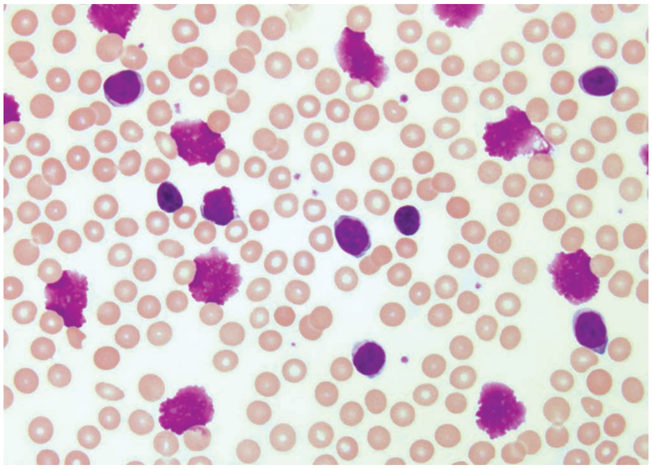

Figure VI.Q9.

What is the best next step in management?
a. Observation
b. R-CHOP

c. Lenalidomide and dexamethasone
d. Imatinib

VI.10. A 65-year-old man seeks care for right leg swelling and pain 6 weeks after right total knee arthroplasty. He did not receive heparin deep vein thrombosis (DVT) prophylaxis while in the hospital and was dismissed taking aspirin for DVT prophylaxis with instructions to discontinue it after 4 weeks. He has a history of hyperlipidemia and hypertension, for which he is taking atorvastatin and hydrochlorothiazide. Physical examination demonstrates swelling and tenderness of the right thigh and a healed surgical scar on his right knee. Doppler ultrasonography documents a right femoral DVT. Laboratory analysis shows normal results of serum tests of renal and hepatic function and a normal complete blood cell count. Which of the following is the most appropriate anticoagulation strategy?

a. Low-molecular-weight heparin with transition to rivaroxaban
b. Dabigatran
c. Low-molecular-weight heparin with transition to warfarin
d. Low-molecular-weight heparin with transition to apixaban

VI.11. A 60-year-old woman is scheduled to undergo elective laparoscopic cholecystectomy for cholelithiasis. She has no chronic illnesses and is not currently taking any medications. Other than mild tenderness in her right upper quadrant, results of her physical examination are normal. Results of serum liver and renal function tests are normal, as are the complete blood cell count and prothrombin time (international normalized ratio). Her activated partial thromboplastin time is prolonged, and subsequent work-up demonstrates a lupus anticoagulant. She undergoes an uneventful cholecystectomy and receives venous thrombosis prophylaxis while hospitalized. She is now being referred for follow-up management. What is the most appropriate next step in management?

a. Observation
b. Apixaban
c. Dabigatran
d. Glucocorticoids

VI.12. A 70-year-old woman seeks care for left leg swelling and pain 3 weeks after left total hip arthroplasty. She has a history of hypertension, for which she is taking enalapril. Physical examination demonstrates swelling and tenderness of the left thigh and a healed surgical scar. Laboratory investigations indicate normal results of serum tests of renal and hepatic function and complete blood cell count. Doppler ultrasonography documents a left femoral deep vein thrombosis. Careful review of hospital records shows that she did not receive heparin deep vein thrombosis prophylaxis while in the hospital. Anticoagulation with apixaban is initiated. What is the most appropriate duration of anticoagulation for this patient?

a. 3 months
b. 6 months
c. 12 months
d. Long term

Answers

VI.1. Answer d.

Measurement of serum ferritin is the most useful initial test for iron deficiency. A ferritin level less than 15 mcg/L almost always indicates iron deficiency. The reticulocyte count is low in iron deficiency and several other conditions, such as marrow failure, intrinsic RBC synthetic defects, and vitamin B_{12}/folate deficiencies. Serum iron level and transferrin saturation will be low and TIBC will be high in iron deficiency, which help in distinguishing it from anemia of chronic disease, but they are not diagnostic of the condition. ESR and CRP are inflammatory markers that are normal in iron deficiency anemia.

VI.2. Answer b.

Hydroxyurea, a myelosuppressive agent, is the only effective drug to reduce the frequency of painful episodes. It increases the level of hemoglobin F and, hence, the hemoglobin level. It usually decreases the rate of painful episodes by 50%. Transfusion of red blood cells to above the patient's baseline level should be avoided because more painful episodes occur with higher hemoglobin levels. Opioids and intravenous hydration are helpful aspects of management during an acute pain crisis but have a minimal role in preventing future episodes.

VI.3. Answer c.

The mild anemia and microcytosis out of proportion to the degree of anemia indicate a diagnosis of thalassemia. In addition, the RBC count is increased and the RDW is normal, which also suggest thalassemia. Iron deficiency anemia is also microcytic but has a low RBC count and a high RDW. Anemia of chronic disease is typically normocytic but can be mildly microcytic and is seen in association with chronic diseases such as chronic renal disease or autoimmune disorders. Sideroblastic anemias are characterized by microcytic, normocytic, or macrocytic anemia and ring sideroblasts in the bone marrow and are often seen in myelodysplastic syndromes. Reactive causes include alcohol and drugs such as isoniazid and pyrazinamide.

VI.4. Answer c.

Given that there is a hereditary component to this patient's bleeding disorder and it has an autosomal inheritance pattern, the most likely diagnosis is von Willebrand disease, which is also the most common hereditary bleeding disorder. Factor VII testing is not indicated given the normal prothrombin time. Given that the aPTT is normal, factor IX and factor VIII inhibitor testing are not indicated.

VI.5. Answer c.

In the initial evaluation for thrombocytopenia, before ordering additional sophisticated testing, pseudothrombocytopenia must be excluded. Pseudothrombocytopenia is due to in vitro platelet clumping mediated by EDTA. This may be excluded by performing a peripheral blood smear to look for platelet aggregates or repeating the CBC with the specimen collected in citrate rather than EDTA. Until pseudothrombocytopenia is excluded, additional invasive and noninvasive tests are not indicated.

VI.6. Answer a.

This patient's clinical picture is consistent with chronic autoimmune thrombocytopenia. Her platelet count has remained essentially stable and she has had no serious bleeding problems. Therefore, continued observation is reasonable, without the need for additional investigation or therapy.

VI.7. Answer c.

The patient has acute myeloid leukemia with a dangerously high WBC, with symptoms concerning for leukostasis. Emergent leukapheresis is necessary. Packed red blood cell transfusion, intravenous dexamethasone, or plateletpheresis would not be the first steps in treating leukostasis.

VI.8. Answer d.

This patient has chronic myelogenous leukemia characterized by the 9;22 translocation ("Philadelphia chromosome"), which results in an abnormal fusion of the *BCR* and *ABL* genes. Tyrosine kinase inhibitors such as imatinib are standard first-line therapies. Therapy with 7+3 is classically used in the treatment of acute myeloid leukemia. R-CHOP is typically used in the treatment of lymphomas. Lenalidomide is used for patients with del(5q) myelodysplastic syndrome, who have a favorable prognosis and respond well to treatment.

VI.9. Answer a.

This asymptomatic patient has chronic lymphocytic leukemia with normal hemoglobin and platelet levels. Early treatment does not improve survival in this disease; therefore, observation is recommended. R-CHOP is typically used in the treatment of lymphomas. Patients with del(5q) myelodysplastic syndrome have a favorable prognosis and respond well to lenalidomide treatment. Imatinib is often used in the treatment of chronic myelogenous leukemia.

VI.10. Answer c.

For management of acute venous thrombosis, initial heparin therapy is required before transition to warfarin, dabigatran, or edoxaban. Initial heparin therapy is not required before starting rivaroxaban or apixaban.

VI.11. Answer a.

In this case, the lupus anticoagulant was discovered incidentally. She has not previously had venous or arterial thrombosis, so neither long-term anticoagulation nor any sort of immune suppression is indicated. Follow-up testing in 12 weeks to document persistence of the lupus anticoagulant is indicated. Long-term management consists of providing venous thromboembolism prophylaxis in appropriate high-risk situations.

VI.12. Answer a.

Venous thromboembolism occurring in association with a temporary risk factor such as hip arthroplasty requires only 3 months of anticoagulation.

Section

VII

Infectious Diseases

43

Central Nervous System Infections

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Bacterial Meningitis

Acute bacterial meningitis is an infectious disease emergency. The incidence of bacterial meningitis is estimated to be 3.0 cases per 100,000 person-years, and its overall case fatality rate is 25% in adults. Common predisposing conditions for community-acquired meningitis include acute otitis media, altered immune states, alcoholism, pneumonia, diabetes mellitus, sinusitis, and a cerebrospinal fluid (CSF) leak. Risk factors for death among adults with community-acquired meningitis include age 60 years or older, altered mental status at presentation, pneumococcal cause, and occurrence of seizures within 24 hours of symptom onset. In two-thirds of patients, classic features of fever and nuchal rigidity are present.

The organisms most commonly causing community-acquired meningitis in adults are *Streptococcus pneumoniae* (38%), *Neisseria meningitidis* (14%), *Listeria monocytogenes* (11%), streptococci (7%), *Staphylococcus aureus* (5%), *Haemophilus influenzae* (4%), and gram-negative bacilli (4%).

When meningitis is suspected, indications for computed tomography before lumbar puncture include immunocompromise, new-onset seizures, papilledema, altered consciousness, or focal neurologic deficits. Radiographic testing should not delay commencement of empirical antimicrobial therapy.

Typical CSF characteristics in bacterial meningitis include a white blood cell count of 1,000 to 5,000/mcL and a glucose value less than 40 mg/dL or CSF to serum glucose ratio of less than 0.4. The differential blood cell count is likely to show a predominance of neutrophils. Gram stain is positive in 60% to 90% of cases. Countercurrent immunoelectrophoresis or latex agglutination tests may provide results in 15 minutes and are useful for the detection of *H influenzae* type B; *S pneumoniae; N meningitidis* types A, B, C, and Y; *Escherichia coli* K1; and group B streptococci in the absence of a positive Gram stain, although these tests are no longer routinely performed. Multiplex polymerase chain reaction testing can provide a rapid specific result, although false-positive results have been reported. CSF culture results are positive in 70% to 85% of cases if testing is done before antibiotic therapy. Blood cultures may be helpful for establishing the diagnosis and should be routinely performed whenever bacterial meningitis is suspected, ideally before initiation of empirical antibiotic therapy.

Management of suspected community-acquired bacterial meningitis is outlined in Figure 43.1. Recommendations for antimicrobial therapy are listed in Table 43.1. Causative organisms, affected age-groups, and predisposing factors in bacterial meningitis are listed in Table 43.2, and empirical treatment in various age-groups and patient groups is outlined in Table 43.3.

Treatment guidelines from the Infectious Diseases Society of America suggest a role for dexamethasone use in the early treatment of suspected pneumococcal meningitis in adults. Of note, corticosteroids are beneficial when administered either concurrently or before antimicrobial therapy. When it is subsequently determined that the patient does not have pneumococcal meningitis, dexamethasone therapy should be discontinued.

KEY FACTS

- ✓ Acute bacterial meningitis is an infectious disease emergency
- ✓ In adults, the most common cause of community-acquired meningitis is *S pneumoniae*
- ✓ When meningitis is suspected, computed tomography is indicated before lumbar puncture in patients with the following characteristics: age >60 years, immunocompromised, new-onset seizures, papilledema, altered consciousness, or focal neurologic deficits
- ✓ Typical characteristics of CSF in bacterial meningitis include a white blood cell count of 1,000-5,000/mcL and glucose level <40 mg/dL
- ✓ In bacterial meningitis, the differential blood cell count is likely to show a high proportion of neutrophils

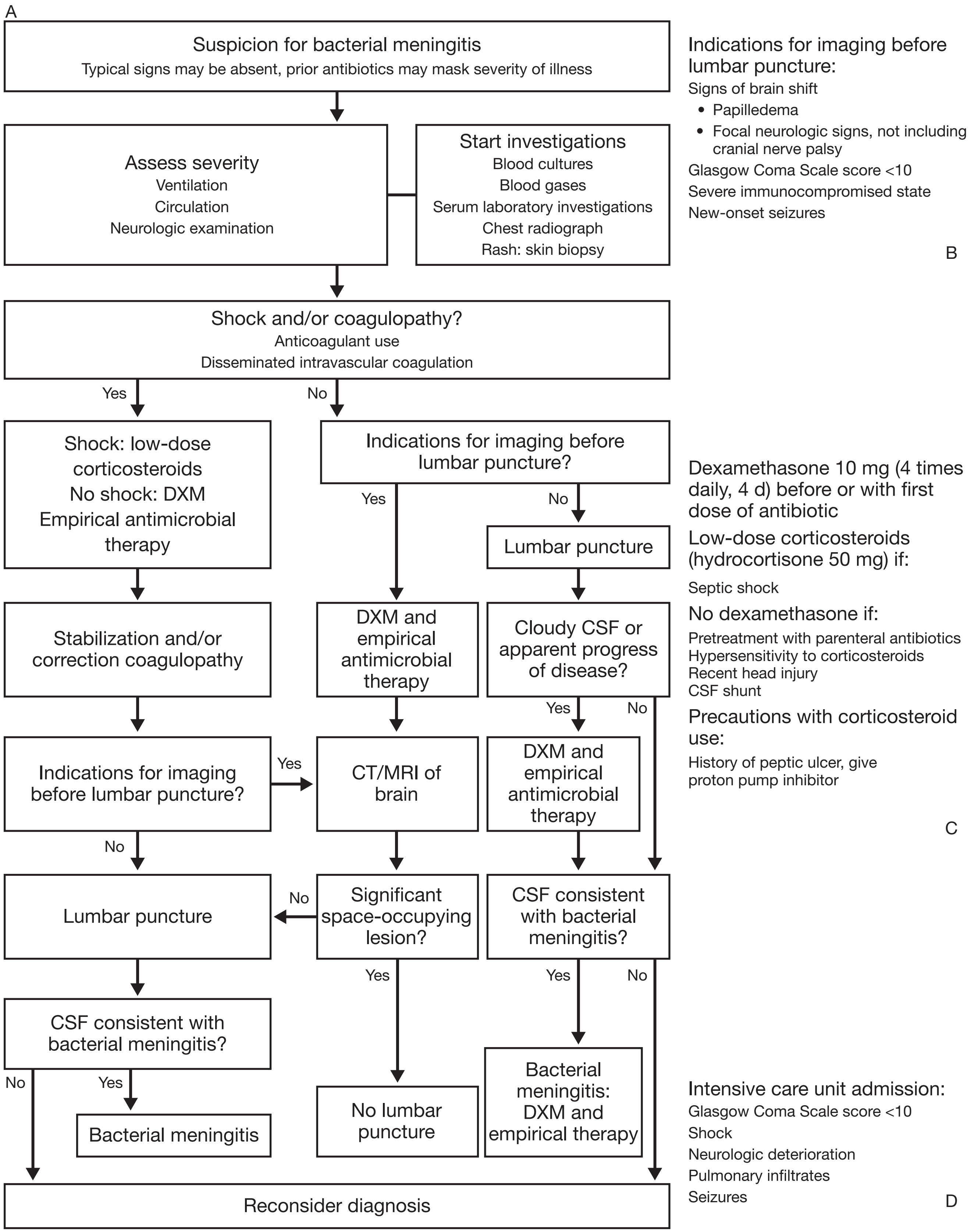
A
Suspicion for bacterial meningitis
Typical signs may be absent, prior antibiotics may mask severity of illness
Assess severity
Ventilation
Circulation
Neurologic examination
Start investigations
Blood cultures
Blood gases
Serum laboratory investigations
Chest radiograph
Rash: skin biopsy
Shock and/or coagulopathy?
Anticoagulant use
Disseminated intravascular coagulation
Yes
No
Shock: low-dose corticosteroids
No shock: DXM
Empirical antimicrobial therapy
Indications for imaging before lumbar puncture?
Yes
No
Lumbar puncture
Stabilization and/or correction coagulopathy
DXM and empirical antimicrobial therapy
Cloudy CSF or apparent progress of disease?
Yes
No
Indications for imaging before lumbar puncture?
Yes
CT/MRI of brain
DXM and empirical antimicrobial therapy
No
Lumbar puncture
No
Significant space-occupying lesion?
CSF consistent with bacterial meningitis?
Yes
Yes
No
CSF consistent with bacterial meningitis?
No
Yes
Bacterial meningitis
No lumbar puncture
Bacterial meningitis: DXM and empirical therapy
Reconsider diagnosis
Indications for imaging before lumbar puncture:
Signs of brain shift
• Papilledema
• Focal neurologic signs, not including cranial nerve palsy
Glasgow Coma Scale score <10
Severe immunocompromised state
New-onset seizures
B
Dexamethasone 10 mg (4 times daily, 4 d) before or with first dose of antibiotic
Low-dose corticosteroids (hydrocortisone 50 mg) if:
Septic shock
No dexamethasone if:
Pretreatment with parenteral antibiotics
Hypersensitivity to corticosteroids
Recent head injury
CSF shunt
Precautions with corticosteroid use:
History of peptic ulcer, give proton pump inhibitor
C
Intensive care unit admission:
Glasgow Coma Scale score <10
Shock
Neurologic deterioration
Pulmonary infiltrates
Seizures
D

Figure 43.1. *Management of Suspected Community-Acquired Bacterial Meningitis. A, Algorithm for initial treatment of adults with bacterial meningitis. B, Indications for performing imaging before lumbar puncture. C, Recommendations for adjunctive dexamethasone therapy in adults with bacterial meningitis. D, Criteria for admission of patients with bacterial meningitis to the intensive care unit. CSF indicates cerebrospinal fluid; CT, computed tomography; DXM, dexamethasone; MRI, magnetic resonance imaging.*

(From van de Beek D, de Gans J, Tunkel AR, Wijdicks EFM. Community-acquired bacterial meningitis in adults. N Engl J Med. 2006 Jan 5;[Suppl Appendix]354[1]:44-53; used with permission.)

Table 43.1 • Recommendations for Antimicrobial Therapy in Adults With Community-Acquired Bacterial Meningitis

Empirical Therapy

Predisposing Factor	Common Bacterial Pathogen	Antimicrobial Therapy
Age, y		
16-50	*Neisseria meningitidis, Streptococcus pneumoniae*	Vancomycin plus a third-generation cephalosporin[a,b]
>50	*S pneumoniae, N meningitidis, Listeria monocytogenes*	Vancomycin plus a third-generation cephalosporin plus ampicillin[b,c]
With risk factor present[d]	*S pneumoniae, L monocytogenes, Haemophilus influenza*	Vancomycin plus a third-generation cephalosporin plus ampicillin[b,c]

Specific Antimicrobial Therapy

Microorganism, Susceptibility	Standard Therapy	Alternative Therapy
S pneumoniae		
Penicillin MIC		
<0.1 mg/L	Penicillin G or ampicillin	Third-generation cephalosporin,[b] chloramphenicol
0.1-1.0 mg/L	Third-generation cephalosporin[b]	Cefepime, meropenem
≥2.0 mg/L	Vancomycin plus a third-generation cephalosporin[b,e]	Fluoroquinolone[f]
Cefotaxime or ceftriaxone MIC		
≥1.0 mg/L	Vancomycin plus a third-generation cephalosporin[b,g]	Fluoroquinolone[f]
N meningitides		
Penicillin MIC		
<0.1 mg/L	Penicillin G or ampicillin	Third-generation cephalosporin,[b] chloramphenicol
0.1-1.0 mg/L	Third-generation cephalosporin[b]	Chloramphenicol, fluoroquinolone, meropenem
L monocytogenes	Penicillin G or ampicillin[h]	Trimethoprim-sulfamethoxazole, meropenem
Group B streptococcus	Penicillin G or ampicillin[h]	Third-generation cephalosporin[b]
Escherichia coli and other *Enterobacteriaceae*	Third-generation cephalosporin[b]	Aztreonam, fluoroquinolone, meropenem, trimethoprim-sulfamethoxazole, ampicillin
Staphylococcus		
Methicillin-sensitive	Nafcillin or oxacillin	Vancomycin
Methicillin-resistant	Vancomycin	Daptomycin, trimethoprim-sulfamethoxazole, or linezolid
Pseudomonas aeruginosa	Ceftazidime or cefepime[h]	Aztreonam,[h] ciprofloxacin,[h] meropenem[h]
H influenza		
β-Lactamase negative	Ampicillin, third-generation cephalosporin,[b] cefepime, chloramphenicol, fluoroquinolone	
β-Lactamase positive	Third-generation cephalosporin[b]	Cefepime, chloramphenicol, fluoroquinolone

Abbreviation: MIC, minimal inhibitory concentration.

[a] Only in areas with very low rate of penicillin resistance (<1%) should monotherapy with penicillin be considered, although many experts recommend combination therapy for all patients until results of in vitro susceptibility testing are known.

[b] Cefotaxime or ceftriaxone.

[c] Only in areas with very low rates of penicillin resistance and cephalosporin resistance should combination therapy of amoxicillin (ampicillin) and a third-generation cephalosporin be considered.

[d] Alcoholism, altered immune status.

[e] Consider addition of rifampicin (rifampin) when dexamethasone is given.

[f] Gatifloxacin or moxifloxacin; no clinical data on use in patients with bacterial meningitis.

[g] Consider addition of rifampicin (rifampin) when the MIC of ceftriaxone is 2 mg/L or more.

[h] Consider addition of an aminoglycoside.

Note: The duration of therapy for patients with bacterial meningitis has often been based more on tradition than on evidence-based data and needs to be individualized on the basis of a patient's response. In general, antimicrobial therapy is given for 7 days for meningitis caused by *N meningitidis* and *H influenzae*, 10 to 14 days for *S pneumoniae*, and at least 21 days for *L monocytogenes*.

From van de Beek D, de Gans J, Tunkel AR, Wijdicks EFM. Community-acquired bacterial meningitis in adults. N Engl J Med. 2006 Jan 5;354(1):44-53; used with permission.

Table 43.2 • Organisms Involved, Affected Age-groups, and Predisposing Factors in Bacterial Meningitis

Organism	Risk Group	Comment	Predisposing Factors
Streptococcus pneumoniae	Any age, but often advanced age	Most common cause of recurrent meningitis in adults	Cerebrospinal fluid leak, alcoholism, splenectomy, functional asplenia, multiple myeloma, hypogammaglobulinemia, Hodgkin disease, HIV infection
Neisseria meningitidis	Infants to 40 y	Petechial rash common Epidemics in closed populations	Terminal component complement deficiency
Haemophilus influenzae, type B	Infants to 6 y	Significant decrease in incidence since licensure of *H influenzae* B vaccine	Hypogammaglobulinemia in adults, HIV infection, splenectomy, functional asplenia
Escherichia coli, group B streptococci	Neonates		Maternal colonization
Gram-negative bacilli	Any age	*Staphylococcus aureus* and coagulase-negative staphylococci also common after neurosurgical procedure	Neurosurgical procedures; bacteremia due to urinary tract infection, pneumonia, and other conditions; *Strongyloides* hyperinfection syndrome
Listeria monocytogenes	Neonates; immunosuppressed persons		

Meningococcus

Neisseria meningitidis is a gram-negative diplococcus that is carried in the nasopharynx of otherwise healthy persons. Because of widespread use of *H influenzae* vaccination in children, *N meningitidis* has emerged as a leading cause of bacterial meningitis in children and young adults. Most sporadic cases (95%-97%) are caused by serogroups B, C, and Y, whereas A and C strains are usually observed in epidemics. Risk factors for meningococcal infection include host and environmental factors. Host characteristics include terminal complement component (C5-C9) deficiency, which increases infection rates but is associated with low mortality rates. The organism is spread through respiratory droplets from asymptomatic pharyngeal carriers. Risk factors include a preceding viral respiratory infection; crowding in a household, barracks, or dormitory; chronic medical illnesses; corticosteroid use; and active or passive smoking. Travel to the "meningitis belt" of north central Africa or to the Hajj in Saudi Arabia is a risk factor for meningococcal meningitis, and vaccination is recommended before travel to these areas.

Neisseria meningitidis infection often begins with a mild upper respiratory tract illness that may disseminate into the bloodstream. A petechial rash often occurs around the same time as fever and meningeal signs. The diagnosis can be made by visualizing the small gram-negative diplococci on a CSF

Table 43.3 • Empirical Therapy for Bacterial Meningitis

Age-group/Patient Group	Common Pathogens	Antimicrobial Therapy
Age		
0-4 wk	Group B streptococci, *Escherichia coli, Listeria monocytogenes, Klebsiella pneumoniae, Enterococcus* spp, *Salmonella* spp	Ampicillin plus cefotaxime or ampicillin plus an aminoglycoside
1-23 mo	Group B streptococci, *E coli, L monocytogenes, Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis*	Vancomycin plus cefotaxime or ceftriaxone
2-50 y	*N meningitidis, S pneumoniae*	Vancomycin plus cefotaxime or ceftriaxone
>50 y	*S pneumoniae, L monocytogenes*, aerobic gram-negative bacilli	Vancomycin plus either cefotaxime or ceftriaxone plus ampicillin (cephalosporins have **no** activity against *Listeria*)
Basilar skull fracture	*S pneumoniae, H influenzae*, group A β-hemolytic streptococci	Vancomycin plus cefotaxime or ceftriaxone
Postneurosurgery	Coagulase-negative staphylococci, *Staphylococcus aureus*, aerobic gram-negative bacilli (including *Pseudomonas aeruginosa*)	Vancomycin plus cefepime or ceftazidime or meropenem

Modified from Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. 2004 Nov 1;39(9):1267-84; used with permission.

Gram stain. The preferred therapy for meningococcal meningitis is high-dose ceftriaxone or cefotaxime given for 7 days (Table 43.1). Penicillin G can be used effectively when the minimum inhibitory concentration is less than 0.1 mcg/mL.

Persons in close contact with the index case (eg, hospital workers with direct exposure to respiratory secretions during intubation, roommates, persons in the same household, day-care center members, persons exposed to the patient's oral secretions) should be offered chemoprophylaxis, ideally within 24 hours of exposure. For adults, ciprofloxacin (500 mg, oral, single dose), ceftriaxone (250 mg, intramuscularly, single dose), or rifampin (600 mg, oral, twice daily for 2 days) is recommended. Rare cases of ciprofloxacin-resistant *N meningitidis* have been reported. Because penicillin does not eliminate the carrier state, the index patient may require a prophylaxis regimen for its eradication if penicillin G is used for treatment. Immunization of certain populations (eg, military recruits, college students living in dormitories, Hajj pilgrims, patients with terminal complement component deficiencies or asplenia) is also recommended. Two meningococcal vaccines are currently available for serogroups A, C, Y, and W-135: the older polysaccharide vaccine and a newer conjugate vaccine, a meningococcal vaccine (MCV4) that offers longer protection. The MCV4 vaccine is now recommended as part of the routine vaccine series in children. Two meningococcal serogroup B vaccines are available and are recommended for use during outbreaks, in persons at increased risk for meningococcal infection, and in young adults (16-23 years).

KEY FACTS

- ✓ *Neisseria meningitidis* infection often begins with a mild upper respiratory tract illness that may disseminate into the bloodstream; a petechial rash often occurs around the same time as fever and meningeal signs
- ✓ Meningococcal immunization is recommended for military recruits; college students living in dormitories; pilgrims from Hajj, Saudi Arabia; and patients with terminal complement component deficiency or asplenia

Pneumococcus

Streptococcus pneumoniae is the most common cause of bacterial meningitis in adults (Figure 43.2), including those with recurrent meningitis due to CSF leaks. Meningitis due to a susceptible strain of *S pneumoniae* can still be treated successfully with high-dose penicillin G. However, given the spread of penicillin-resistant strains, bacterial meningitis should be empirically treated with high-dose cefotaxime or ceftriaxone in combination with vancomycin while susceptibility results are awaited (Table 43.1). Adjunctive treatment with dexamethasone has been shown to be beneficial when started at the same time as or before the first dose of antibiotic. The recommended treatment duration for pneumococcal meningitis is 10 to 14 days.

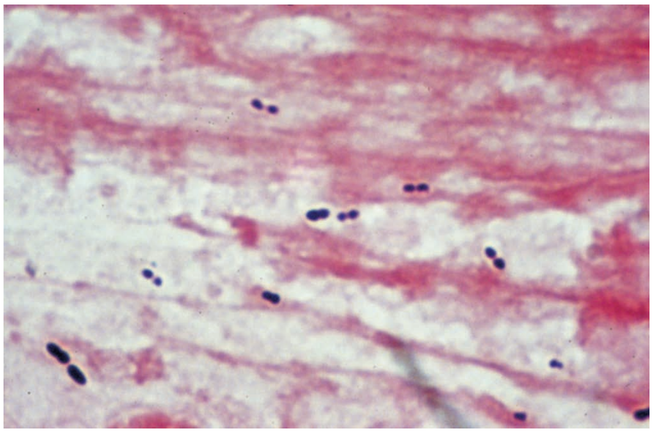

Figure 43.2. *Gram Stain of* Streptococcus pneumoniae *in Sputum.*

Haemophilus influenza

Widespread use of the vaccine against *H influenzae* type B has dramatically reduced the incidence of this invasive disease in children. Infections caused by *H influenzae* include pneumonia, meningitis, epiglottitis, sinusitis, otitis media, primary bacteremia, and infectious exacerbations of chronic obstructive pulmonary disease. Chronic lung disease, pregnancy, HIV infection, hypogammaglobulinemia, splenectomy, and malignancy are risk factors for invasive disease.

Infection with *H influenzae* is now an uncommon cause of meningitis in adults, although it can occur with hypogammaglobulinemia, asplenia, or CSF leak. For treatment of *H influenzae* meningitis, third-generation cephalosporins (cefotaxime or ceftriaxone) are given for 7 days.

Listeria

Listeria monocytogenes is a small, motile, gram-positive rod. Meningitis and bacteremia are the most common syndromes of invasive *Listeria* infection. Elderly persons, neonates, pregnant women, and immunocompromised persons (eg, persons taking corticosteroids) are at highest risk for invasive disease due to *Listeria*. Epidemics have been associated with consumption of contaminated dairy products, some ready-to-eat foods such as hot dogs and luncheon meats, contaminated stone fruits, and prepackaged caramel apples. Diarrhea is usually a feature of epidemic listeriosis. *Listeria* meningitis is often subacute. The organism may be difficult to visualize, and the result of CSF Gram stain is positive in only 25% to 30% of cases.

Penicillin and ampicillin are the most effective agents against *Listeria*. Ampicillin should be included in the empiric coverage of meningitis in patients older than 50 years or those who are immunosuppressed because *Listeria* is always resistant to cephalosporins. Combination therapy with an aminoglycoside is often recommended for treatment of severe disease. Trimethoprim-sulfamethoxazole is an effective alternative for the penicillin-allergic patient. Recommended treatment duration for *Listeria* meningitis is 3 weeks.

Group B β-Hemolytic Streptococci: *Streptococcus agalactiae*

This organism, a frequent part of the normal flora of the genital and gastrointestinal tracts, is an important cause of postpartum maternal and neonatal infections. It also is an important cause of bacteremia and metastatic infection in elderly adults, especially nursing home residents and those with chronic underlying diseases such as diabetes. β-Lactams are the treatment of choice for infections caused by *S agalactiae*. Meningitis, which most commonly occurs in neonates, is best treated with penicillin (or ampicillin) plus gentamicin. Women whose prepartum vaginal or rectal swab culture identifies group B streptococcus pose a high risk for early neonatal group B streptococcal infection, and tartgeted intrapartum antimicrobial prophylaxis should be given at onset of labor.

Brain Abscess

Brain abscess is defined as a focal infection within the brain parenchyma. Two primary mechanisms of infection are hematogenous spread and contiguous spread of infection. Brain abscesses that form as a result of hematogenous spread tend to present as multifocal abscesses. Primary infectious causes in the setting of bacteremia include infectious endocarditis, skin and soft tissue infection, pulmonary abscess, and pelvic or intra-abdominal infection. Congenital cardiac abnormalities including cardiac shunts may increase the risk of hematogenous seeding of the brain. Primary sites of infection for contiguous spread are sinus infection, dental infection, or otitis media or mastoiditis. Brain abscess can also occur after neurosurgical procedures or trauma.

The microbiologic causes of community-onset brain abscess reflect the primary site of infection. The most common causes are *Streptococci* species (sinus, odontogenic, otogenic source) and *Staphylococci.* Various opportunistic pathogens should be considered in the differential diagnosis in immunocompromised patients, including *Nocardia, Listeria, Toxoplasma*, fungal disease, and mycobacterial disease.

Clinical manifestations include headache and localizing features (hemiparesis, unilateral cranial nerve deficits) on physical examination. Fever is not always present, and altered mental status and vomiting are indicative of increased intracranial pressure. In all cases of suspected brain abscess, neuroimaging should be done before lumbar puncture given its potential risk of brainstem herniation.

Imaging establishes the diagnosis of brain abscess, and magnetic resonance imaging is the method of choice. A microbiologic diagnosis can be established with computed tomography–guided aspiration or surgical biopsy. The sample should be evaluated with Gram stain, aerobic and anaerobic bacterial cultures, fungal and mycobacterial stain and cultures, and special stains on histopathologic analysis.

Definitive treatment of brain abscess usually involves a combination of intravenous antimicrobials (targeting the identified pathogen) and a surgical approach for drainage of abscess (computed tomography–guided or open). Duration of antibiotic therapy for bacterial brain abscess is usually prolonged, 4 to 8 weeks. A longer course is recommended when treatment has not included drainage of the abscess.

Aseptic Meningitis and Encephalitis

Aseptic meningitis syndrome is characterized by an acute onset of meningeal symptoms, fever, CSF pleocytosis (usually lymphocytic), and negative results of CSF bacterial cultures. Noninfectious causes include medications, such as nonsteroidal anti-inflammatory drugs and trimethoprim-sulfamethoxazole; chemical meningitis; and neoplastic meningitis. Often, this syndrome is a meningoencephalitis due to viruses, which can be differentiated by an accurate exposure history and seasonality (Table 43.4).

Table 43.4 • Epidemiologic Clues to Infectious Causes of Acute Aseptic Meningitis and Meningoencephalitis

Season, Exposure, and Risk Factors	**Pathogens**
Late summer or fall	Enteroviruses
Winter	Mumps
Rodent urine	Lymphocytic choriomeningitis virus
Mosquito bites	Eastern and Western Equine viruses, West Nile virus, St. Louis virus, La Crosse virus
Ticks	*Borrelia burgdorferi, Ehrlichia*, or *Anaplasma* infection, Rocky Mountain spotted fever
Risk factors for sexually transmitted infections	Herpes simplex virus or human immunodeficiency virus
Immunocompromise	*Cryptococcus neoformans*
Travel to endemic area	Histoplasmosis, blastomycosis, coccidioidomycosis, Japanese encephalitis virus, yellow fever, rabies, tickborne encephalitis

The CSF should always be analyzed in cases of suspected meningoencephalitis. The following tests may be helpful: cultures for bacteria and fungi and polymerase chain reaction assays for herpes simplex virus, Epstein-Barr virus, varicella zoster virus, the enteroviruses, and *Mycobacterium tuberculosis*. CSF and serum antigen tests for *Cryptococcus neoformans* and urine antigen tests for *Histoplasma* or *Blastomyces* may be useful in the appropriate clinical setting. *Treponema pallidum* (syphilis) and *Borrelia burgdorferi* (Lyme disease) infections can be detected with the CSF VDRL test and serum *B burgdorferi*–specific antibody test, respectively. When there is a clinical suspicion of herpes simplex virus encephalitis but results on initial polymerase chain reaction assay of CSF for herpes simplex virus are negative, repeat testing in 1 to 3 days may yield positive results if clinical suspicion remains high. Besides CSF testing, blood tests may be helpful for establishing a cause of encephalitis. Serologic testing for HIV, Epstein-Barr virus, and *Mycoplasma pneumoniae* may be useful. Depending on the patient's epidemiologic exposure, additional serologic tests on serum samples may be indicated (Table 43.4).

Imaging may be helpful for establishing a cause of encephalitis. Magnetic resonance imaging may localize findings in specific infections such as herpes simplex virus encephalitis (which localizes to the temporal lobes) (Figure 43.3). Electroencephalography can be helpful for identifying patients with nonconvulsive seizure activity who are confused, obtunded, or comatose. It shows characteristic periodic, lateralized epileptiform discharges in herpes simplex virus encephalitis.

Empirical therapy for encephalitis should always include early administration of intravenous high-dose acyclovir, given its considerable mortality benefit with prompt treatment of herpes simplex virus encephalitis. In addition, empiric antibacterials directed at bacterial meningitis should be added until bacterial meningitis has been ruled out. Doxycycline should be added initially when risk factors for tick-borne illness such as *Borrelia* (Lyme), *Rickettsia*, or *Ehrlichia* infection are present. After an etiologic agent is identified, therapy should be targeted to that pathogen and the use of other antimicrobial agents should be discontinued. Recommended treatment duration for herpes simplex virus encephalitis is 14 to 21 days.

Chronic Meningitis Syndrome

Signs and symptoms of meningeal inflammation are more subtle in chronic meningitis and evolve over weeks to months. Chronic meningitis may be due to either infectious or noninfectious causes. Delayed presentation with apathy or altered mentation can occur. The CSF profile typically shows long-term inflammatory changes. The causative agents of chronic meningitis due to infection include *Brucella, Nocardia*, spirochetes (eg, syphilis, Lyme disease), fungi (eg, *Cryptococcus, Coccidioides, Histoplasma, Blastomyces*), mycobacteria, and parasites.

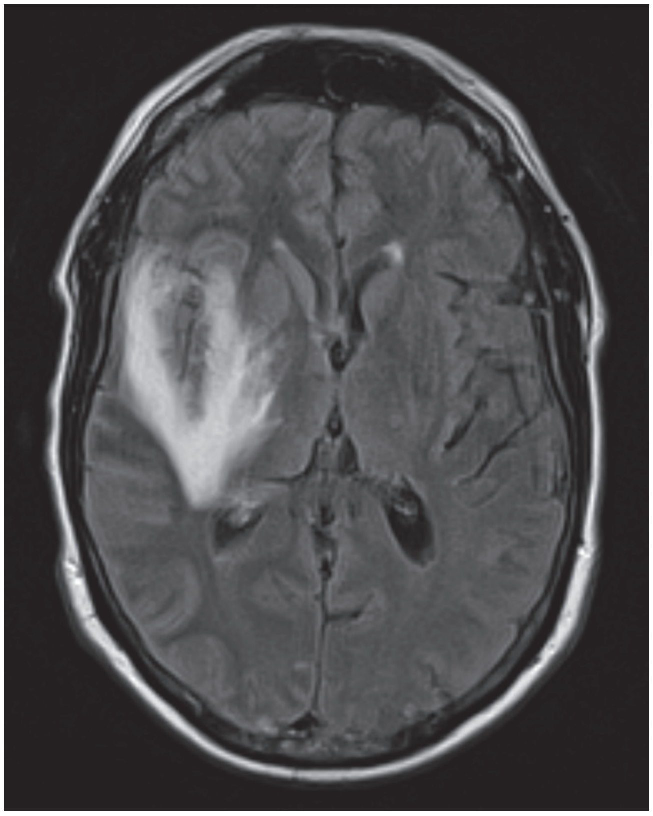

Figure 43.3. *Magnetic Resonance Image of Herpes Simplex Virus Encephalitis Localized in the Temporal Lobe.*

(From Smith H, Gaillard F, et al. Herpes simplex encephalitis [Internet]. Radiopaedia.org. c2019 Dr Frank Gaillard [cited 2019 Jan 15]. Available from: http://radiopaedia.org/articles/herpes-simplex-encephalitis; used with permission.)

KEY FACTS

✓ Aseptic meningitis syndrome involves acute onset of meningeal symptoms, fever, CSF pleocytosis, and negative results of CSF bacterial cultures

✓ Empirical therapy for encephalitis should always include intravenous high-dose acyclovir and antibiotics, including doxycycline when risk factors for *Rickettsia* or *Ehrlichia* infection are present

Other Causes of Central Nervous System Infections

Poliovirus

Although wild-type polio has been eliminated from the Western Hemisphere, it continues to be endemic in parts of Asia and Africa. Polio is most often an asymptomatic infection.

The virus affects the nuclei of cranial nerves and anterior motor neurons of the spinal cord, causing a flaccid paralysis, usually asymmetrical. In the United States, a poliolike illness that is not associated with personal travel or exposure should raise suspicion for West Nile virus.

Rabies

A requisite for an antemortem diagnosis of rabies is a strong suspicion. Cardinal clinical manifestations are hydrophobia and copious salivation. Rabies should be considered in any case of encephalitis or myelitis of unknown cause, especially in persons who have recently traveled outside the United States. The virus spreads along peripheral nerves to the central nervous system. The most common source of exposure in the world is dogs; in the United States, bats, foxes, raccoons, and skunks are often implicated.

Rabies acquisition in the United States is predominantly related to bat bites, which may not be apparent, especially when they occur during sleep. Annually, 1 or 2 cases of rabies are reported in the United States. Definitive diagnosis of rabies encephalitis is established by finding Negri bodies on biopsy of the hippocampus. Serum and CSF can be tested for rabies antibodies when trying to diagnose the disease. Direct fluorescent antibody testing of a skin biopsy specimen from the nape of the neck can be used to detect rabies antigen.

Any bite by bats or other animals suspected of carrying rabies should be taken seriously. Postbite management includes observing the animal, if possible, immediate soap and water washing of the wound, administering rabies immunoglobulin (injected into the bite site), and starting the postexposure rabies vaccine schedule (4 doses given at days 0, 3, 7, and 14 after the bite). Preexposure rabies vaccination series is advised for patients likely to be in situations that put them at high risk for rabies, such as occupational exposure in veterinary medicine, spelunking, and prolonged stay in rabies-endemic countries. Preexposure vaccination mitigates the need for rabies immunoglobulin and decreases the number of postexposure vaccine doses to 2, given at days 0 and 3 after the bite.

Slow Viruses and Prion-Associated Central Nervous System Diseases

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy is caused by a papovavirus (JC virus) and usually occurs in immunocompromised patients, such as those with AIDS, leukemia, or lymphoma; in patients taking certain medications (eg, natalizumab for multiple sclerosis); and patients who are immunosuppressed for organ transplant. It can cause either diffuse or focal central nervous system abnormalities. Imaging findings show multifocal white matter areas with changes of demyelination. Results of CSF analysis are normal in most cases, and the diagnosis is based on brain biopsy. Detection of JC virus DNA in CSF with polymerase chain reaction testing in appropriate clinical context confirms the diagnosis. However, the sensitivity of this test is low. There is no effective therapy directed at the JC virus. However, antiretroviral drugs in patients with AIDS and reduction of immunosuppression in transplant patients or otherwise immunosuppressed patients usually lead to improvement.

Creutzfeldt-Jakob Disease

This is a rare degenerative and fatal disease of the central nervous system. It occurs equally in both sexes, usually at older ages. The disease has both familial and sporadic forms. It usually presents as rapidly evolving dementia with myoclonic seizures. **Prions** (small proteinaceous infectious particles without nucleic acid) have been proposed as the cause of this disease. Nosocomial transmission of Creutzfeldt-Jakob disease can occur from corneal transplant and exposure to CSF. Creutzfeldt-Jakob disease has no treatment.

Key Definitions

Creutzfeldt-Jakob disease: *A rare degenerative and fatal disease of the central nervous system with familial and sporadic forms for which there is no treatment.*

Prions: *Small proteinaceous infectious particles without nucleic acid.*

Epidural Abscess

The most common location of this suppurative CNS infection is the spine, and intracranial location is less common. Intracranial epidural abscesses, like brain abscesses, can follow surgical procedures, as well as otitis, mastoiditis, sinusitis, and dental abscesses.

Spinal epidural abscess can be classified into nosocomial and community-acquired infection. The most commonly identified pathogen is *S aureus* in both types of infection, and infections due to streptococci, coagulase-negative staphylococci, gram-negative bacilli, and anaerobes also occur. Nosocomial infections are most commonly due to direct inoculation of microorganisms during an invasive procedure or operative intervention or to hematogenous spread of infection. Nonprocedure-related cases are most commonly caused by a hematogenous source, and contiguous infection (eg, complex intra-abdominal or pelvic infections) is less likely.

Establishing a microbiologic diagnosis is essential to optimize medical management. If patients are systemically and neurologically stable at presentation, empirical antimicrobials should not be given until culture specimens are obtained. These include blood and those obtained with image-guided abscess aspiration (such as computed tomography–guided aspiration). Empirical antimicrobials should be broad pending the culture data and should provide activity against methicillin-resistant *S aureus* and gram-negative organisms, including *Pseudomonas* (eg, cefepime and vancomycin). If a spinal epidural abscess is putting direct pressure on the spinal cord, permanent neurologic complications or even death can occur. If such deficits are present, spinal epidural abscess is a neurologic or surgical emergency, and immediate neurologic decompression and empirical antibiotic therapy should be considered.

Duration of therapy is not well defined. Typically, a 4- to 8-week (usually 6 weeks) course with culture-directed intravenous therapy is recommended. Duration is guided by clinical response and by improvement in inflammatory markers, including erythrocyte sedimentation rate, and C-reactive protein. Serial imaging to document improvement is generally not recommended because of the frequent lag in radiologic improvement. Duration of antimicrobial management also depends on whether a medical-only or image-guided aspiration or drainage or surgical drainage or decompression is pursued. Studies of spinal infections have indicated that those caused by epidural abscesses have poor outcomes. Close clinical follow-up is required in cases managed nonoperatively.

Iatrogenic and Postoperative Central Nervous System Infections

The epidemiologic factors of health care–associated meningitis and ventriculitis vary considerably in terms of causative microorganisms from community-onset infections. Health care–associated meningitis includes postprocedural (eg, CSF shunts, deep brain stimulators), head trauma, and neurosurgical cases. The Infectious Diseases Society of America released updated guidelines in 2017 for the management of health care–associated ventriculitis and meningitis. Of most importance are potential differences and difficulties in establishing the microbiologic diagnosis. The most common causative organisms include staphylococci, including methicillin-resistant *S aureus*, and gram-negative rods, including *Pseudomonas*. Other multidrug-resistant gram-negative bacilli may also be causes.

Diagnosis

Presenting signs and symptoms may include headache, nausea, lethargy, seizures, signs of meningeal irritation, or altered mental status. Fever may not always be present. Neuroimaging is recommended in all patients suspected to have health care–associated ventriculitis and meningitis. Specimens for blood cultures should be obtained in all cases. A CSF analysis is recommended to evaluate for cell count, glucose and protein values, and culture. Hypoglycorrhachia, increased CSF protein value, increasing CSF pleocytosis, and positive culture results are indicative of infection. Additional factors that may help differentiate CSF abnormalities due to a recent procedure, surgery, or infection include CSF lactate and CSF procalcitonin levels, particularly because some CSF abnormalities may result from a postoperative inflammatory state. In cases of suspected fungal infection, β-D-glucan and galactomannan in CSF may be useful for diagnosis of fungal meningitis.

Management

Empirical antibacterial management of health care–associated meningitis should provide coverage for methicillin-resistant *S aureus* such as vancomycin, and an anti-pseudomonal β-lactam (eg, cefepime, ceftazidime, meropenem). Empirical treatment options are listed in Table 43.3. Selected antimicrobials should have the ability to cross the blood-brain barrier to reach appropriate levels in the central nervous system. Once culture results are available, antibiotic therapy should be adjusted on the basis of culture and susceptibility data. Duration of antimicrobial therapy is somewhat pathogen-dependent. Although a shorter course of 10 to 14 days is considered reasonable for coagulase-negative staphylococci, *Propionibacterium acnes*, or *S aureus*, this duration is typically extended to 21 days for gram-negative organisms.

In addition to appropriate antimicrobial therapy, infected devices (such as ventriculoperitoneal shunt, ventriculoatrial shunt, or deep brain stimulators) should be removed.

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HIV Infection[a]

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Transmission

HIV is transmitted sexually, perinatally, through parenteral inoculation (eg, intravenous drug injection, occupational exposure), through blood products, and, less commonly, through donated organs or semen (Table 44.1). Sexual transmission is the most common means of infection. Conditions that may increase the risk of sexually acquiring HIV infection include traumatic intercourse (ie, receptive anal), ulcerative genital infections (including syphilis, herpes simplex, and chancroid), and lack of male circumcision. The proper use of latex condoms substantially reduces the risk of HIV transmission. Nonoxynol spermicide increases the risk of HIV transmission; therefore, condoms that do not contain spermicide are preferred for HIV prevention. Condoms with spermicide do offer some protection compared with not using a condom, however. Perinatal transmission can occur in utero, at birth, and through breast milk.

Laboratory Diagnosis

The Centers for Disease Control and Prevention (CDC) updated the testing algorithm for diagnosing HIV in 2014 (Figure 44.1). The recommended testing is a combination immunoassay that detects HIV-1 and HIV-2 antibodies and HIV p24 antigen. Positive specimens undergo secondary testing to differentiate HIV-1 antibodies from HIV-2 antibodies. Specimens that are negative or indeterminate on this secondary testing undergo HIV-1 nucleic acid testing for resolution. Specimens that are negative on the nucleic acid testing are considered to be false-positive results. This testing sequence provides a more accurate diagnosis of acute HIV than previous screening that involved only antibody testing. The combined immunoassay has an increased likelihood of positive results because of the presence of p24 antigen in the serum, usually by 15 days after infection.

The CDC and the US Preventive Services Task Force both recommend that screening for HIV infection be performed routinely for all patients 13 to 64 years old. An opt-out approach, similar to what has been used successfully for many years with pregnant women, is recommended. With the opt-out approach, testing is performed after the patient is notified, unless the patient declines. Neither separate written consent nor prevention counseling is required.

Patients who engage in behaviors that place them at risk for HIV infection should be screened on a regular basis. All pregnant

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[a] Portions previously published in Warnke D, Barreto J, Temesgen Z. J Clin Pharmacol. 2007 Dec;47(12):1570-9; used with permission; Panel on Antiretroviral Guidelines for Adults and Adolescents. Department of Health and Human Services. [cited 2019 Jan 24.] Available from http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf; Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. [cited 2019 Jan 24.] Available from http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf; Preexposure prophylaxis for the prevention of HIV infection in the United States—2014. [cited 2019 Jan 24.] Available from https://aidsetc.org/resource/preexposure-prophylaxis-prevention-hiv-infection-united-states-2014; and Centers for Disease Control and Prevention. [cited 2019 Jan 24.] Available from: https://www.cdc.gov/hiv/pdf/programresources/cdc-hiv-npep-guidelines.pdf.

Table 44.1 • Risk of HIV Infection by Type of Exposure

Type of Exposure	Risk, %
Transfusion of HIV-positive blood	>90
Percutaneous needlestick	0.3
Receptive anal intercourse	0.5
Receptive penile-vaginal intercourse	0.1
Insertive intercourse	0.05-0.07
Oral intercourse	0.005-0.01
Blood to mucous membranes	0.09
Blood to nonintact skin	<0.1

women should be screened for HIV infection with each pregnancy. Chronic HIV infection should be considered in patients with many different presentations; some of the more common clues are listed in Box 44.1.

KEY FACTS

✓ The CDC updated the testing algorithm for diagnosing HIV infection in 2014. The recommended testing is a combination immunoassay that detects HIV-1 and HIV-2 antibodies and HIV p24 antigen

✓ The current testing sequence provides a more accurate diagnosis of acute HIV than previous screening that involved only antibody testing. The combination immunoassay has fewer false-negative results because of the presence of p24 antigen in the serum by 15 days after infection

✓ The CDC and the US Preventive Services Task Force both recommend that screening for HIV infection be performed routinely for all patients aged 13 to 64 years

✓ All pregnant women should be screened for HIV infection with each pregnancy

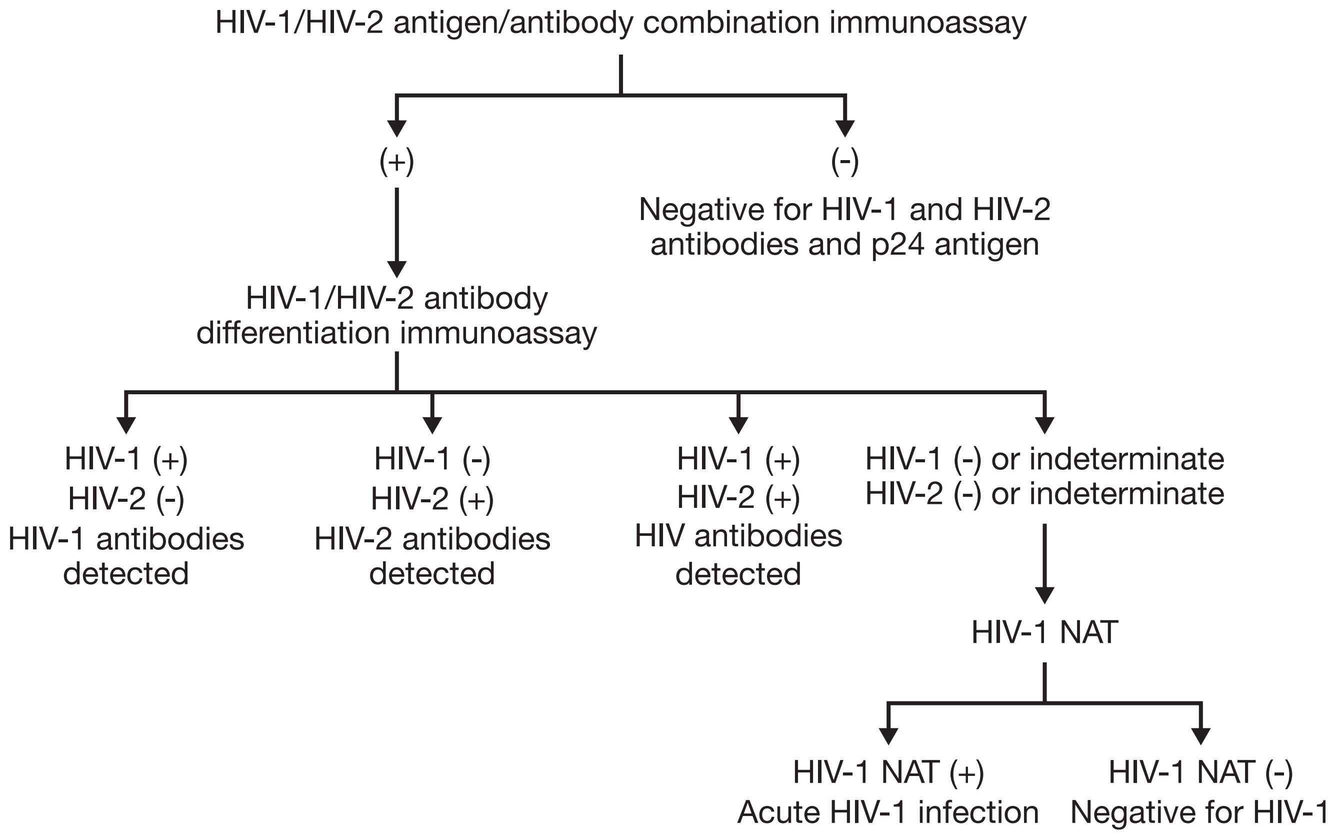
HIV-1/HIV-2 antigen/antibody combination immunoassay
(+)
(-)
Negative for HIV-1 and HIV-2 antibodies and p24 antigen
HIV-1/HIV-2 antibody differentiation immunoassay
HIV-1 (+) HIV-2 (-) HIV-1 antibodies detected
HIV-1 (-) HIV-2 (+) HIV-2 antibodies detected
HIV-1 (+) HIV-2 (+) HIV antibodies detected
HIV-1 (-) or indeterminate HIV-2 (-) or indeterminate
HIV-1 NAT
HIV-1 NAT (+) Acute HIV-1 infection
HIV-1 NAT (-) Negative for HIV-1

Figure 44.1. Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens. NAT indicates nucleic acid test; +, reactive test result; –, nonreactive test result.

(From Centers for Disease Control and Prevention and National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. Laboratory testing for the diagnosis of HIV infection: updated recommendations. Published June 27, 2014 [Updated 2018 Jan; cited 2019 Jan 24] Available from http://stacks.cdc.gov/view/cdc/23447.)

Box 44.1 • Common Clinical Clues to Chronic HIV Infection

- History of high-risk behavior
- History of a sexually transmitted disease
- Request for HIV testing
- Active tuberculosis
- Herpes zoster in a person <50 y old
- New severe flare of psoriasis
- Unexplained severe skin disorder
- Hepatitis B or C virus infection
- Cervical cancer or HPV infection
- Thrush not related to recent antibiotic use
- Unexplained cachexia or weight loss
- Diffuse lymphadenopathy
- Unexplained thrombocytopenia, leukopenia, or anemia
- Unusual neurologic illness
- History of unusual infection in an otherwise healthy person
- Prolonged unexplained illness

Abbreviation: HPV, human papillomavirus.

Modified from Kasten MJ. Human immunodeficiency virus: the initial physician-patient encounter. Mayo Clin Proc. 2002 Sep;77(9):957-63; used with permission of Mayo Foundation for Medical Education and Research.

Natural History of HIV Disease

Acute HIV Infection

Days to weeks after exposure to HIV, most infected persons present with a brief illness that may last from a few days to a few weeks. This period of illness is associated with an enormous amount of circulating virus, a rapid decline in the CD4 cell count, and a vigorous immune response. Occasionally, CD4 counts decrease to levels at which patients can present with opportunistic illness. Patients often present with a mononucleosis-like illness, but the clinical manifestations of acute HIV infection are extremely varied (Table 44.2).

Chronic HIV Infection

After acute HIV infection, CD4 counts rebound, although frequently not to baseline, and the viral load decreases to a set point that often stays stable for years. Over time, most patients have a gradual loss of CD4 cells. Some patients continue to be asymptomatic with relatively preserved CD4 counts for more than a decade; other patients progress to AIDS in 2 to 3 years. The loss of CD4 cells eventually places the person at risk for opportunistic infections and other complications of HIV infection. The CDC defines **AIDS** as known HIV infection with a CD4 count less than 200 cells/mcL or HIV infection associated with an AIDS-defining illness (Box 44.2).

Table 44.2 • Frequency of Symptoms and Findings Associated With Acute HIV-1 Infection

Symptom or Finding	Patients, %
Fever	>80-90
Fatigue	>70-90
Rash	>40-80
Headache	32-70
Lymphadenopathy	40-70
Pharyngitis	50-70
Myalgia or arthralgia	50-70
Nausea, vomiting, or diarrhea	30-60
Night sweats	50
Aseptic meningitis	24
Oral ulcers	10-20
Genital ulcers	5-15
Thrombocytopenia	45
Leukopenia	40
Increased hepatic enzyme levels	21

From Kahn JO, Walker BD. Acute human immunodeficiency virus type 1 infection. N Engl J Med. 1998 Jul 2;339(1):33-9; used with permission.

Key Definition

AIDS: *known HIV infection with a CD4 count <200 cells/mcL or HIV infection associated with an AIDS-defining illness.*

The illnesses and conditions associated with HIV infection vary greatly depending on a person's CD4 count and behaviors. Figure 44.2 illustrates the natural history of HIV infection and the stages at which conditions that are commonly associated with HIV infection occur.

KEY FACTS

- ✓ Patients often present with a mononucleosis-like illness, but the clinical manifestations of acute HIV infection are extremely varied
- ✓ The CDC defines AIDS as known HIV infection with a CD4 count <200 cells/mcL or HIV infection associated with an AIDS-defining illness

Box 44.2 • AIDS-Defining Conditions in Adults

Candidiasis of bronchi, trachea, or lungs
Candidiasis, esophageal
Cervical cancer, invasive
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 mo duration)
CMV disease (other than liver, spleen, or nodes)
CMV retinitis (with loss of vision)
Encephalopathy, HIV-related
Herpes simplex: chronic ulcer(s) (>1 mo duration) or bronchitis, pneumonitis, or esophagitis
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 mo duration)
Kaposi sarcoma
Lymphoma, Burkitt (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
Mycobacterium tuberculosis, any site
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jiroveci pneumonia
Pneumonia, recurrent
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain
Wasting syndrome due to HIV infection

Abbreviation: CMV, cytomegalovirus.

Data from Schneider E, Whitmore S, Glynn MK, Dominguez K, Mitsch A, McKenna MT. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years—United States, 2008. MMWR Morb Mortal Wkly Rep. 2008 Dec 5;57(RR10):1-8.

Primary Care and HIV Infection

Immunizations

Patients with HIV infection should have routine immunizations, but live virus vaccines should be given cautiously and generally are avoided in patients with CD4 counts less than 200 cells/mcL. For patients who were immunized when they had low CD4 cell counts, clinicians should consider repeating immunizations after the immune system has improved.

All patients with HIV infection who are not immune to or infected with hepatitis B virus should receive the hepatitis B vaccination series. Antibody response to the hepatitis B vaccine is poorer in HIV-infected patients than noninfected patients, and a "double-dose" vaccine is recommended. Antibody response to the vaccination should be verified after the series is completed. Deferring this vaccination series until the patient's CD4 count is more than 200 cells/mcL is reasonable for improvement of response rates.

Hepatitis A vaccine is recommended for all patients who are at risk, including men who have sex with men, travelers to developing countries, and patients with hepatitis B or C or other liver disease.

All adults infected with HIV should receive a conjugate meningococcal vaccine, 2 doses given 8 weeks or more apart. A booster dose should be administered every 5 years.

All patients with HIV infection should receive the pneumococcal conjugate vaccine (PCV13) unless they have received a dose of pneumococcal polysaccharide vaccine-23 (PPV23) within the past year. These patients should receive the PCV13 a year after their PPV23. If a patient has not had the PPV23 and has a CD4 count of more than 200 cells/mcL, the PCV13 should be given and should be followed with the PPV23 at 8 or more weeks later. A second dose of PPV23 should be given 5 or more years after the first dose. Many providers defer PPV23 in HIV-infected patients until their CD4 count improves, ideally to more than 200 cells/mcL.

The quadrivalent human papillomavirus vaccine is recommended for HIV-infected women and men between ages 11 and 26 years.

All HIV-infected patients should receive an annual inactivated influenza vaccine.

Prophylaxis Against Opportunistic Infections

HIV-infected persons are susceptible to many unusual infections, depending on their CD4 counts. A few of these infections can be prevented with immunization or appropriate prophylaxis. Recommendations and indications for primary prevention of *Pneumocystis* pneumonia (PCP), *Mycobacterium avium* complex (MAC) infection, and toxoplasmosis are listed in Table 44.3. Primary prophylaxis against other infections is not routinely recommended; primary prophylaxis against PCP and toxoplasmosis can be discontinued when the CD4 count is 200 cells/mcL or more for 3 months or longer. Primary prophylaxis against MAC can be discontinued when the CD4 count is 100 cells/mcL or more for 3 months or longer.

Cancer Screening

Three cancers—Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer—have been designated as AIDS-defining cancers. Several other malignancies, although not classified as *AIDS-defining*, seem to be more common among people infected with HIV. HIV-infected patients who are generally well, whether or not receiving antiretroviral treatment, should have routine cancer screening as recommended for uninfected persons, with the exception of the need for more frequent Papanicolaou (Pap) smears. Women with HIV infection should have a cervical Pap smear at the time of diagnosis.

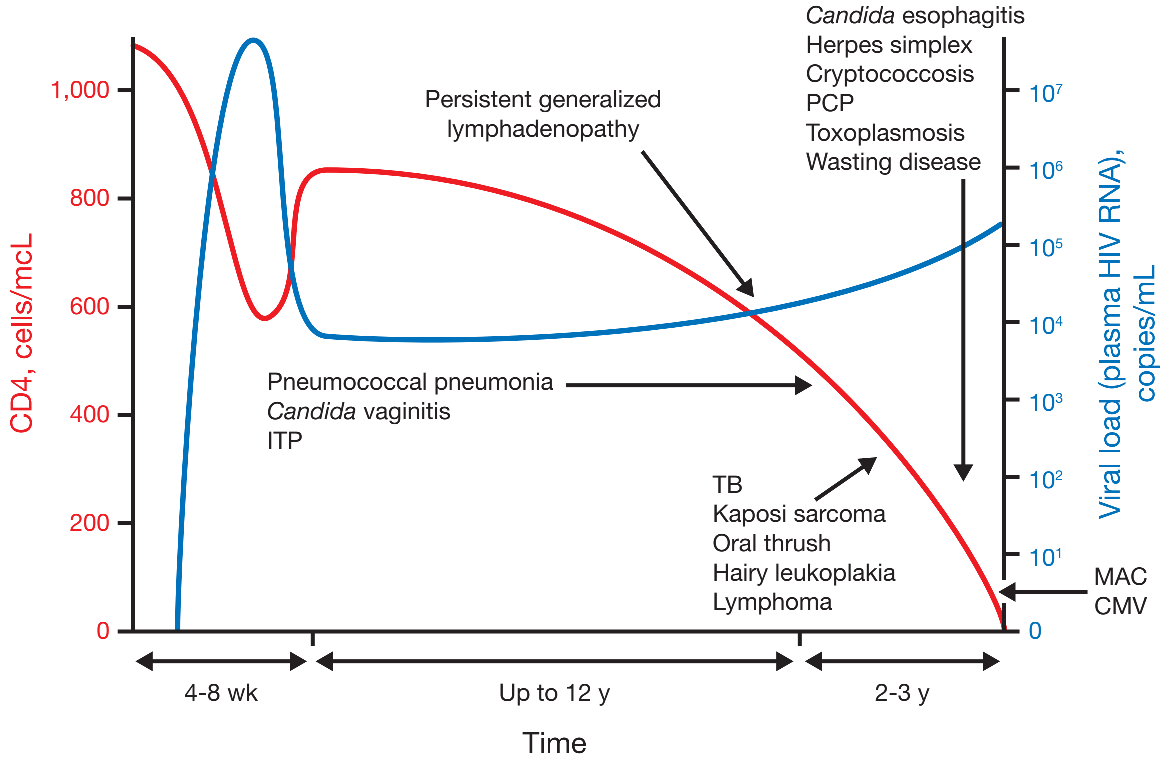

Figure 44.2. *Natural History of HIV Infection: CD4 Counts, Viral Load, and Clinical Manifestations. CMV indicates cytomegalovirus; ITP, idiopathic thrombocytopenic purpura; MAC,* Mycobacterium avium *complex; PCP,* Pneumocystis *pneumonia; TB, tuberculosis.*

Cotesting—Pap smear and human papillomavirus testing—is not recommended for HIV-infected women younger than 30 years. When Pap smears alone are used for cervical cancer screening, the test should be repeated in 12 months if the result is normal. After results of Pap smears are normal 3 consecutive times, testing can decrease to every 3 years if results continue to be normal. Women older than 30 years can be screened with cotesting, and if results are normal, screening every 3 years is recommended. HIV-infected women should have continued screening with either Pap smears or cotesting even after age 65 years, unlike the general population. HIV-infected women with abnormal results of Pap smears should be monitored by a practitioner with expertise in preventing cervical cancer in HIV infection. An anal Pap smear should be considered for men and women who have a history of receptive anal intercourse, an abnormal result of Pap smear, or a history of genital warts because of the increased incidence of human papillomavirus–related anal cell cancer.

Table 44.3 • Primary Prophylaxis for PCP, Toxoplasmosis, and MAC

Pathogen/Disease	Indication	First-Choice Therapy
Pneumocystis jiroveci/PCP	CD4 <200 cells/mcL or oropharyngeal candidiasis	TMP-SMX
Toxoplasma gondii/encephalitis	*Toxoplasma* IgG-positive with CD4 <100 cells/mcL	TMP-SMX DS
MAC/MAC disease	CD4 <50 cells/mcL after ruling out active MAC infection	Azithromycin *or* clarithromycin

Abbreviations: DS, double strength; IgG, immunoglobulin G; MAC, *Mycobacterium avium* complex; PCP, *Pneumocystis* pneumonia; TMP-SMX, trimethoprim-sulfamethoxazole.

Data from Kaplan JE, Benson C, Holmes KK, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Morb Mortal Wkly Rep. 2009 Apr 10;58(RR04):1-198.

KEY FACT

✓ HIV-infected women should have a cervical Pap smear at the time of diagnosis. Cotesting—Pap smear and human papillomavirus testing—is not recommended for HIV-infected women younger than 30 years. When Pap smears alone are used for cervical screening, the test should be repeated in 12 months if the result is normal

Selected AIDS-Associated Malignancies

Kaposi Sarcoma

Kaposi sarcoma, a vascular tumor, is an AIDS-defining illness and is most common in men who have sex with men. Human herpesvirus 8, also known as Kaposi sarcoma–associated herpesvirus, has been established as the etiologic agent of Kaposi sarcoma. Human herpesvirus 8 appears to be sexually transmitted. With HIV, it synergistically acts to induce the changes of Kaposi sarcoma. Histologically, whorls of spindle-shaped cells and abnormal proliferation of small blood vessels are seen. Skin, lung, and the gastrointestinal tract are the commonly affected organs. Early on, skin lesions are often mistaken for benign vascular lesions.

Key Definition

Kaposi sarcoma: *a vascular cancerous tumor that is AIDS-defining.*

Treatment options include antiretroviral therapy, local therapy (eg, radiotherapy, intralesional chemotherapy, cryotherapy), and systemic therapy (eg, chemotherapy, interferon-α). Liposome-encapsulated anthracycline chemotherapeutic agents enable delivery of high doses of effective drug with fewer adverse effects than with other agents. ART has resulted in a substantial reduction in the incidence of Kaposi sarcoma and has been associated with a reduction in tumor burden and disease progression. Occasionally, ART-immune reconstitution exacerbates Kaposi sarcoma, causing an inflammatory and therefore more symptomatic disease. ART is first-line therapy for nonvisceral disease. The benefit of ART in HIV-associated Kaposi sarcoma is clear, and it is recommended for all HIV-infected patients with Kaposi sarcoma.

Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma is much more common (as high as a 200-fold increased risk) among HIV-infected patients than in the general population. It is a heterogeneous group of malignancies with varying biologic behavior and occurs in patients with widely ranging levels of immune function. The vast majority of non-Hodgkin lymphomas in patients with HIV infection are of B-cell origin. Intermediate- or high-grade B-cell non-Hodgkin lymphoma in a patient with HIV infection is a CDC-defined AIDS diagnosis. As patients with AIDS live longer, this complication is likely to become more frequent. Non-Hodgkin lymphomas commonly present with constitutional symptoms (fever, night sweats, and weight loss), lymphadenopathy, and involvement of extranodal sites, such as the central nervous system, bone marrow, gastrointestinal tract, and liver. Involvement of the brain in non-Hodgkin lymphoma can manifest as an isolated disease (primary central nervous system lymphoma) or as leptomeningeal involvement in the context of spread of lymphoma elsewhere.

The optimal treatment of HIV-associated non-Hodgkin lymphoma has not been well defined. Current recommendations suggest that most patients should receive standard-dose chemotherapy, PCP prophylaxis (regardless of CD4 count), and growth factor support. In addition, highly active ART should be a component of therapy.

KEY FACT

✓ Non-Hodgkin lymphoma is much more common (as high as a 200-fold increased risk) among HIV-infected patients than in the general population

Selected Infections and Conditions Associated With HIV Infection

Pneumocystis Pneumonia

PCP is one of the most common opportunistic infections in patients with AIDS. It typically occurs in patients with CD4 counts less than 200 cells/mcL. The onset of illness is usually insidious, with several days to weeks of fever, exertional dyspnea, chest discomfort, weight loss, malaise, and night sweats. Chest radiography typically shows bilateral interstitial pulmonary infiltrates; a lobar distribution and spontaneous pneumothoraces may also occur. Patients with early disease can have a normal result on chest radiography. Thin-section computed tomography usually shows patchy ground-glass infiltrates. Arterial blood gas analysis usually shows hypoxemia and respiratory alkalosis. Levels of 1-3-β-D-glucan levels are increased (>80 pg/mL) and are supportive of a PCP diagnosis.

Definitive diagnosis of PCP is made through visualization of the organism. In HIV-infected persons, staining for *Pneumocystis* organisms in hypertonic saline-induced expectorated sputum is 55% to 90% sensitive, and bronchoalveolar lavage is 90% to 97% sensitive.

The treatment of choice for PCP is trimethoprim-sulfamethoxazole. The usual recommended dosage is 15 mg/kg per day (trimethoprim component) in 3 or 4 equally divided doses for 21 days. If no improvement occurs 4 to 8 days after treatment is begun, a different drug should be considered (Box 44.3). Controlled studies have shown that adjunctive corticosteroid therapy increases survival in patients with moderate to severe disease, defined as room air Po_2 less than 70 mm Hg or an alveolar-arterial Po_2 difference (A-a gradient) more than 35 mm Hg. When indicated, adjunctive corticosteroid therapy should be started immediately; a delay may compromise its effectiveness.

KEY FACTS

- ✓ PCP is one of the most common opportunistic infections in persons with AIDS. It typically occurs in those with CD4 counts <200 cells/mcL
- ✓ The treatment of choice for PCP is trimethoprim-sulfamethoxazole

Tuberculosis

Tuberculosis (TB) is the most common HIV-associated opportunistic infection globally. TB is a preventable disease in patients with HIV infection; all such patients should be screened with either a tuberculin skin test or an interferon-γ release assay. All HIV-infected patients with a positive test result (≥5 mm for the skin test), a past history of a positive test result, or recent exposure to a person with active TB should be treated for latent TB, provided they have no symptoms or signs to suggest active infection and they have not been treated previously. Effective treatment programs for latent TB are reviewed in Box 44.4.

TB occurs among HIV-infected persons at all CD4 counts. However, clinical manifestations generally differ depending on the degree of immunosuppression. When TB occurs late in the course of HIV infection, it tends to have atypical features, such as extrapulmonary disease, disseminated disease, and an unusual chest radiographic appearance (eg, lower lung zone lesions, intrathoracic adenopathy, diffuse infiltrations, lower frequency of cavitation). Patients with low CD4 counts and TB have a high mortality rate (70%) and often have a fulminant course leading to death in 2 to 3 months. When TB occurs early in the course of HIV infection (CD4 count >350 cells/mcL), it tends to manifest with the classic presentation of upper-lobe fibronodular infiltrates with cavitation.

The diagnosis of TB requires evaluation with chest radiography, sputum samples for acid-fast bacillus smear and culture, and aspiration or tissue biopsy when extrapulmonary disease is suspected. Mycobacterial blood cultures are useful in cases of disseminated disease. In patients with relatively intact immune function, the yield of sputum smear and culture is similar to that in HIV-negative patients.

The treatment of HIV-infected patients is complex when they are taking antiretroviral agents and undergoing therapy for active TB. Protease inhibitors and nonnucleoside analogue reverse transcriptase inhibitors have clinically significant interactions with the rifamycins—rifampin, rifabutin, and rifapentine—used to treat mycobacterial infections. TB in HIV-infected persons that is susceptible to all first-line antituberculosis drugs may be treated with the standard 6-month drug program.

Clinicians should consider factors that increase a person's risk of a poor clinical outcome (eg, lack of adherence to TB therapy, delayed conversion of *Mycobacterium tuberculosis* sputum cultures from positive to negative, delayed clinical response) when deciding the total duration of TB therapy. Directly observed therapy is recommended. Patients who have successfully completed a treatment regimen for TB do not require secondary prophylaxis or long-term maintenance therapy. Patients with multiple drug–resistant TB illnesses are at high risk for relapse and treatment failure. Treatment regimens for these patients are complex and require expertise in the management of both TB and HIV infection.

Box 44.3 • Preferred Drug Therapy for PCP

For moderate to severe PCP

- TMP-SMX: 15-20 mg TMP and 75-100 mg SMX/kg daily, IV administered every 6 to 8 h, may switch to orally after clinical improvement
- Duration: 21 d

For mild to moderate PCP

- Same daily dose of TMP-SMX as above, administered orally in 3 divided doses, *or* TMP-SMX (160 mg/800 mg or DS), 2 tablets 3 times daily
- Duration: 21 d

Abbreviations: DS, double strength; IV, intravenously; PCP, *Pneumocystis* pneumonia; TMP-SMX, trimethoprim-sulfamethoxazole.

Data from Kaplan JE, Benson C, Holmes KK, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Morb Mortal Wkly Rep. 2009 Apr 10;58(RR04):1-198.

Box 44.4 • Regimens for the Treatment of Latent Tuberculosis

Isoniazid 300 mg orally daily for 9 mo[a]

Isoniazid 900 mg twice weekly for 9 mo[a]

Rifampin 600 mg orally daily for 4 mo

Isoniazid 15 mg/kg orally once weekly and a weight-based rifapentine dose orally once weekly through directly observed therapy for 12 wk

[a] These regimens are preferred for persons infected with HIV.

KEY FACT

- ✓ All HIV-infected patients with a positive result of tuberculin skin testing (≥5 mm), a past history of a positive test result, or recent exposure to someone with active TB should be treated for latent TB, provided they have no symptoms or signs to suggest active infection and have not been treated previously

MAC Infection

Organisms of MAC are ubiquitous in the environment and include *M avium* and *Mycobacterium intracellulare*. They cause disseminated infection in HIV-infected persons, especially when immunosuppression is severe (CD4 count <50 cells/mcL). Disseminated MAC infection is a common systemic bacterial infection in patients with AIDS and very low CD4 counts. Common presentations include low-grade fever, night sweats, weight loss, fatigue, abdominal pain, and diarrhea. Hepatomegaly, splenomegaly, and lymphadenopathy may be present. Common laboratory abnormalities include anemia and increased alkaline phosphatase levels. Blood cultures are usually positive; however, organisms can also be isolated from stool, respiratory tract secretions, bone marrow, liver, and other biopsy specimens.

The MAC organisms are resistant to conventional antimycobacterial agents. The current recommended treatment regimen includes one of the newer macrolides (eg, clarithromycin, azithromycin), ethambutol, and 1 or 2 additional drugs with activity against MAC.

KEY FACTS

- ✓ Organisms of MAC can cause disseminated infection in HIV-infected persons when immunosuppression is severe (CD4 count <50 cells/mcL)
- ✓ The current recommended treatment regimen includes 1 of the newer macrolides (eg, clarithromycin, azithromycin), ethambutol, and 1 or 2 additional drugs with activity against MAC

Cryptococcus neoformans Disease

Cryptococcus neoformans is a yeast acquired through inhalation. It can cause symptomatic pneumonia, particularly in immunocompromised persons or in persons with lung disease. The organism has a strong propensity for dissemination to the central nervous system. The most common manifestation of *C neoformans* disease in HIV-infected patients is cryptococcal meningitis, which usually occurs when the CD4 count is less than 50 cells/mcL. The onset is insidious; symptoms are nonspecific (eg, fever, headache, malaise) and may have a waxing and waning course. Classic meningeal symptoms (eg, neck stiffness, photophobia) are present in only one-fourth to one-third of patients with HIV and *C neoformans* disease. Brain imaging findings are nonspecific; cerebral atrophy and ventricular enlargement are the most common findings. Cerebrospinal fluid (CSF) findings may be minimal but frequently include increased opening pressure, mild mononuclear pleocytosis, and increased protein value. Glucose levels may be normal or slightly low. The India ink preparation is positive in more than 70% of cases. The serum and CSF cryptococcal antigen tests have a sensitivity of 93% to 99% for cryptococcal meningitis. Cultures of CSF are usually positive. Blood cultures are positive for *C neoformans* in up to 75% of HIV-infected persons with cryptococcal meningitis.

Adverse prognostic factors include altered mental status on presentation and high fungal burden (ie, positive result of India ink test, high antigen titers, and extraneural disease). Increased intracranial pressure is common and may be associated with headache, confusion, or cranial nerve palsies. Aggressive management of intracranial pressure with daily lumbar puncture or placement of lumbar drains substantially minimizes morbidity and death from this illness.

Initial therapy should include amphotericin B with flucytosine for 2 weeks, followed by fluconazole 400 mg daily for a total of 10 weeks. This initial therapy is followed by fluconazole 200 mg daily for long-term maintenance therapy. Such long-term maintenance therapy can be discontinued when the patient continues to be asymptomatic and has a sustained increase in CD4 count to more than 200 cells/mcL for 6 months.

KEY FACTS

- ✓ The most common manifestation of *C neoformans* disease in HIV-infected patients is cryptococcal meningitis, which usually occurs when the CD4 count is <50 cells/mcL
- ✓ Aggressive management of intracranial pressure with daily lumbar puncture or placement of lumbar drains substantially minimizes morbidity and death from this illness
- ✓ Initial therapy should include amphotericin B with flucytosine for 2 weeks, followed by fluconazole 400 mg daily for 10 weeks, which is followed by fluconazole 200 mg daily for long-term maintenance treatment

Cytomegalovirus

Serious cytomegalovirus (CMV) disease does not occur until HIV infection is advanced HIV disease (CD4 count <50 cells/mcL). Other risk factors include previous opportunistic infections and a high plasma HIV-1 RNA level (>100,000 copies/mL). Chorioretinitis is the most common clinical manifestation of CMV in patients with HIV infection. The usual symptoms are floaters, visual field deficits, and painless loss of vision. Funduscopic examination shows yellowish or white retinal infiltrates with or without intraretinal hemorrhage. In CMV gastrointestinal disease, the esophagus and colon are most commonly involved, and the disease manifests with dysphagia, abdominal pain, and bloody diarrhea. Hepatitis, pneumonitis, sclerosing cholangitis, encephalitis, adrenalitis, polyradiculopathy, and myelopathy can also be caused by CMV.

Table 44.4 • Drugs Used for Treatment of CMV Disease

Drug	**Major Adverse Effect**
Systemic anti-CMV therapy	
Ganciclovir IV	Bone marrow suppression
Valganciclovir	Bone marrow suppression
Foscarnet IV	Renal toxicity
Cidofovir IV[a]	Renal toxicity
Local anti-CMV therapy for retinitis	
Ganciclovir intraocular-release device[b]	Retinal detachment
Ganciclovir intravitreal injection[b]	Bone marrow suppression
Foscarnet intravitreal injection[b]	Renal toxicity

Abbreviations: CMV, cytomegalovirus; IV, intravenously.

[a] Vigorous hydration and coadministration of probenecid are required to limit renal toxicity.

[b] Local anti-CMV therapy should be accompanied by systemic therapy, such as oral ganciclovir, to avoid the risk of extraocular diseases.

Agents used for the treatment of CMV disease and their general characteristics are listed in Table 44.4.

All patients with AIDS should undergo annual funduscopic examination to screen for CMV retinitis and other HIV-related eye disease and should have prompt evaluation of reported visual problems. Routine prophylaxis against CMV is not recommended because of concerns regarding treatment-induced toxicities (including neutropenia and anemia), potential resistance, conflicting reports of efficacy, lack of proven survival benefit, and cost.

KEY FACTS

- ✓ CMV disease does not occur until HIV disease is advanced (CD4 count <50 cells/mcL)
- ✓ Chorioretinitis is the most common clinical manifestation of CMV in patients with HIV infection

Toxoplasmosis

Toxoplasma gondii, a protozoan, is the most common cause of focal central nervous system lesions in patients with AIDS. The most common symptoms of *Toxoplasma* encephalitis include headache and confusion; fever may be absent. Focal neurologic deficits occur in 69% of cases. The median CD4 count at diagnosis is 50 cells/mcL. Multiple ring-enhancing lesions with associated edema are usually noted on brain imaging studies. Magnetic resonance imaging is more sensitive than computed tomography for identifying lesions. The differential diagnosis of central nervous system mass lesions in patients with AIDS includes not only toxoplasmosis but also lymphoma and other infections, such as TB, cryptococcosis, histoplasmosis, bacterial abscess, and progressive multifocal leukoencephalitis.

Empirical antitoxoplasmosis therapy is indicated in patients with AIDS and positive *Toxoplasma* serologic testing who present with multiple intracranial lesions. The absence of anti–toxoplasma immunoglobulin G antibody makes a diagnosis of toxoplasmosis unlikely. Effective treatment should result not only in amelioration of symptoms but also in a reduction of the number, size, and contrast medium enhancement of the brain lesions. If the patient has seronegativity for *Toxoplasma*, has a single mass lesion on both computed tomography and magnetic resonance imaging, or did not achieve the desired response after an empirical course of antitoxoplasmosis therapy for 10 to 14 days, the diagnosis of *Toxoplasma* encephalitis should be questioned and a diagnostic brain biopsy considered.

The initial regimen of choice for the treatment of HIV-associated toxoplasmosis is the combination of pyrimethamine plus sulfadiazine plus leucovorin. All HIV-infected persons with a CD4 count of less than 100 cells/mcL who have seropositivity for *Toxoplasma* should receive primary prophylaxis against *Toxoplasma* encephalitis (Table 44.3).

HIV-infected patients should be tested for immunoglobulin G antibody to *Toxoplasma* as part of their initial work-up. If the result is negative, they should be counseled about the various potential sources of *Toxoplasma* infection, including consumption of raw or undercooked meat or shellfish and handling of cat litter.

KEY FACTS

- ✓ *Toxoplasma gondii* is the most common cause of focal central nervous system lesions in patients with AIDS
- ✓ The most common symptoms of *Toxoplasma* encephalitis include headache and confusion; fever may be absent
- ✓ The median CD4 count at diagnosis of toxoplasmosis is 50 cells/mcL
- ✓ Multiple ring-enhancing lesions with associated edema are usually noted on brain imaging studies
- ✓ All HIV-infected persons with a CD4 count of <100 cells/mcL who are seropositive for *Toxoplasma* should receive primary prophylaxis against *Toxoplasma* encephalitis

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy is a demyelinating disease caused by the JC virus, a polyomavirus. The disease occurs primarily with considerable immunosuppression (CD4 count of <200 cells/mcL), but an inflammatory form also occurs with immune reconstitution. Symptoms and signs are progressive, variable, and usually long term or subacute. Symptoms include cognitive dysfunction, dementia, seizures, ataxia, aphasia, cranial nerve deficits, and focal deficits, such as hemiparesis and visual field deficits. Fever is usually absent. Occasionally, symptoms present rapidly and progress in a few weeks to dementia or coma.

Key Definition

Progressive multifocal leukoencephalopathy: *a demyelinating disease caused by JC virus, a polyomavirus.*

Diagnosis is based on clinical findings and magnetic resonance imaging, which shows characteristic white matter changes (bright areas on T2-weighted images) without contrast agent enhancement or mass effect. Routine CSF studies are generally nondiagnostic, but identification of JC virus DNA in the CSF through polymerase chain reaction may confirm the diagnosis. Absence of JC virus DNA does not rule out progressive multifocal leukoencephalopathy.

No specific therapy is established for progressive multifocal leukoencephalopathy. The prognosis has improved considerably with ART, and approximately half of patients with a good response to ART have long-term remission. Thus, all patients with progressive multifocal leukoencephalopathy should be receiving effective ART.

KEY FACTS

- ✓ Progressive multifocal leukoencephalopathy is a demyelinating disease caused by the JC virus
- ✓ Symptoms include cognitive dysfunction, dementia, seizures, ataxia, aphasia, cranial nerve deficits, and focal deficits (eg, hemiparesis, visual field deficits)

Mucocutaneous Candidiasis

Mucocutaneous disease, such as oral thrush, recurrent vaginitis, and candidal esophagitis, is common among HIV-infected persons. Candidal esophagitis is an AIDS-defining condition. Systemic candidal infection, including candidemia, is rare unless additional risk factors for disseminated fungal infection, such as severe neutropenia and indwelling catheters, are present.

Mucocutaneous disease can often be successfully treated with clotrimazole troches or nystatin suspension or pastilles. Fluconazole is used for the treatment of candidal esophagitis and topical treatment failures. Amphotericin B or caspofungin can be used when azoles fail.

Diagnosis of oropharyngeal candidiasis is usually clinical and is based on the appearance of lesions. Visualization of the organisms on microscopic examination of scrapings provides supportive diagnostic information.

Esophageal candidiasis is usually diagnosed presumptively on clinical grounds (retrosternal burning pain or odynophagia in a patient with a low CD4 count or oral candidiasis). A trial of antifungal therapy is recommended before diagnostic endoscopy. Fluconazole, 100 to 400 mg daily, by mouth, is usually used for 14 to 21 days to treat esophageal candidiasis.

Long-term maintenance therapy for recurrent oropharyngeal or vulvovaginal candidiasis is not recommended unless recurrences are frequent or severe. Fluconazole, 100 to 200 mg daily, can be used to prevent esophageal candidiasis or other problematic candidiasis. Azole resistance can occur with long-term use.

KEY FACTS

- ✓ Esophageal candidiasis in HIV-infected patients is usually diagnosed presumptively on clinical grounds (retrosternal burning pain or odynophagia in a patient with a low CD4 count or oral candidiasis)
- ✓ A trial of antifungal therapy is recommended before diagnostic endoscopy

Antiretroviral Agents

The Replication Cycle of HIV

A working knowledge of the HIV replication cycle is essential for understanding the mechanism of action of ART agents. Figure 44.3 reviews the interaction between the virus and the host cell that leads to production of infectious virions.

The 6 classes of antiretroviral drugs are nucleoside and nucleotide analogue reverse transcriptase inhibitors, nonnucleoside analogue reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors, integrase inhibitors, and chemokine coreceptor antagonists. For details about common adverse effects of these medications, see Tables 44.5 through 44.8. A single fusion inhibitor, enfuvirtide, also called *T20*, is available only in an injectable form and causes considerable local site reactions and hypersensitivity reactions. Maraviroc is the only available chemokine coreceptor antagonist and can be used only for patients who have viruses that use the CCR5 receptor for entry into the CD4 cell. This characteristic can be measured with a tropism assay. Both enfuvirtide and maraviroc are used only in salvage programs and therefore are not further discussed.

Guidelines for Use of ART for HIV Infection

Guidelines addressing the use of ART in different populations and situations have been developed and are regularly updated as new information becomes available (http://www.aidsinfo.nih.gov/). The benefits of ART are increasingly

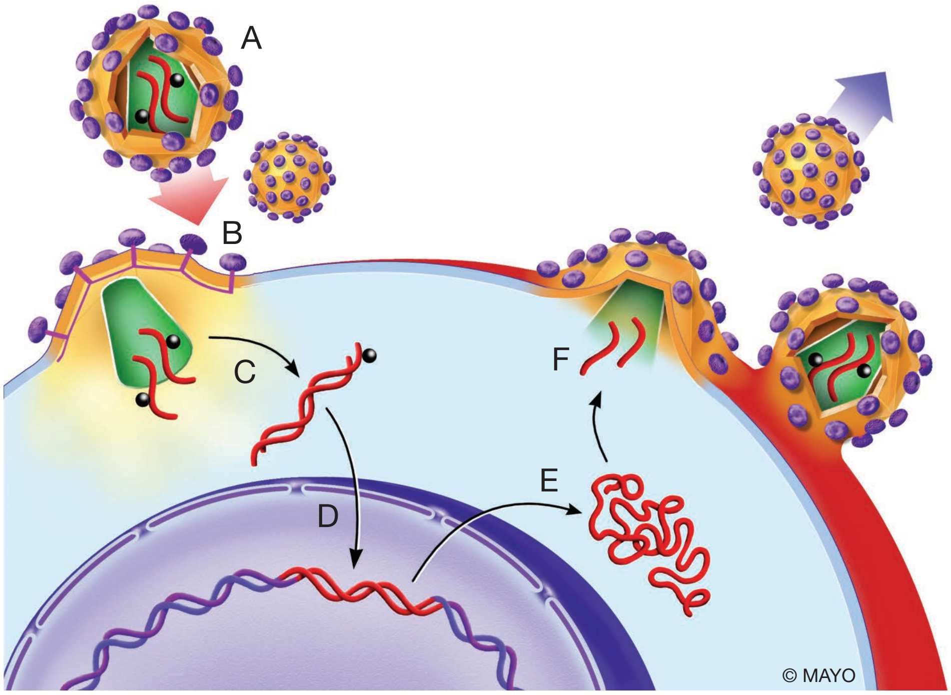

Figure 44.3. *Life Cycle of HIV. A, The virus is an enveloped virus that contains viral genomic RNA and various Gag and Pol protein products. B, The interaction between the envelope proteins of the virus and CD4 receptor and other receptors of the host cell leads to binding of the viral envelope and the host cytoplasmic membrane. C, The viral reverse transcriptase enzyme catalyzes the conversion of viral RNA into DNA. D, The viral DNA enters the nucleus and becomes inserted into the chromosomal DNA of the host cell. E, Expression of the viral genes leads to production of viral RNA and proteins. F, These viral proteins, as well as viral RNA, are assembled at the cell surface into new viral particles and leave the host cell in a process called* budding. *During budding, they acquire the outer layer and envelope. At this stage, the protease enzyme cleaves the precursor Gag and Gag-Pol proteins into their mature products.*

Table 44.5 • Adverse Effects of Nucleoside Analogue Reverse Transcriptase Inhibitors Commonly Used in the United States

Drug Name (Alias)	**Toxic/Adverse Effects**[a]
Abacavir (ABC)	Diarrhea, anorexia, nausea, vomiting, headache, fatigue Contraindicated if HLA-B*5701 negative because of potential for fatal hypersensitivity reactions
Emtricitabine (FTC)	Hyperpigmentation of skin, rash, diarrhea, nausea, vomiting, headache, adverse effects rare
Lamivudine (3TC)	Decrease in appetite, nausea, vomiting, headache, fatigue, adverse effects rare
Tenofovir disaproxil fumarate (TDF)	Diarrhea, nausea, vomiting, osteopenia, renal impairment
Tenofovir alafenamide (TAF)	Gastrointestinal symptoms, headache, adverse effects rare
Zidovudine (ZDV)	Headache, nausea, anorexia, vomiting, anemia, leukopenia, myopathy, lipoatrophy, hyperlipidemia

[a] Lactic acidosis is a class effect that presents with gastrointestinal prodrome and can rapidly progress to organ failure; risk is increased when more nucleoside analogue reverse transcriptase inhibitors are in a program.

Data from Panel on Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services. Oct 17, 2017; [cited 2019 Jan 21]. Available from: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

Table 44.6 • Adverse Effects of Nonnucleoside Analogue Reverse Transcriptase Inhibitors Commonly Used in the United States

Drug Name (Alias)	Toxic/Adverse Effects
Efavirenz (EFV)	Rash, CNS symptoms (dizziness, lightheadedness, abnormal dreams, difficulty with concentration), hepatotoxicity
Etravirine (ETR)	Rash, hypersensitivity reaction
Rilpivirine (RPV)	Headache, insomnia, depression (fewer CNS symptoms than EFV), transient rash, increased transaminase levels, increased total and LDL-C levels, may prolong QT interval Requires acid for absorption

Abbreviations: CNS, central nervous system; LDL-C, low-density lipoprotein cholesterol.

Data from Panel on Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the use of antiretroviral agents in HIV-1–infected adults and adolescents. Department of Health and Human Services. Apr 8, 2015; [cited 2019 Jan 21]. Available from: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

Table 44.7 • Adverse Effects of Protease Inhibitors Commonly Used in the United States

Drug Name (Alias)	Toxic/Adverse Effects[a]
Atazanavir (ATZ)	Indirect hyperbilirubinemia; prolonged PR interval, including symptomatic first-degree AV block; nephrolithiasis; hyperglycemia; fat maldistribution Requires acid for absorption
Darunavir (DRV)	Rash, hepatotoxicity, diarrhea, nausea, headache, hyperlipidemia, transaminase increased, hyperglycemia, fat maldistribution
Lopinavir/ritonavir (LPV/r)	GI tract intolerance, nausea, vomiting, diarrhea, asthenia, hyperlipidemia (especially hypertriglyceridemia), increased serum transaminases, hyperglycemia, fat maldistribution
Ritonavir (RTV)	GI tract intolerance, nausea, vomiting, diarrhea, paresthesias (circumoral and extremities), hyperlipidemia (especially hypertriglyceridemia), hepatitis, asthenia, taste perversion, hyperglycemia, fat maldistribution Used to boost levels of other protease inhibitors
Saquinavir (SQV)	GI tract intolerance, nausea, diarrhea, headache, increased transaminase enzymes, hyperlipidemia, hyperglycemia, fat maldistribution
Tipranavir (TPV)	Hepatotoxicity, including clinical hepatitis; rash; intracranial hemorrhages; hyperlipidemia (especially hypertriglyceridemia); hyperglycemia; fat maldistribution

Abbreviations: AV, atrioventricular; GI, gastrointestinal.

[a] For all drugs listed, increased bleeding episodes are possible in patients with hemophilia.

Data from Panel on Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the use of antiretroviral agents in HIV-1–infected adults and adolescents. Department of Health and Human Services. Apr 8, 2015; [cited 2015 Jul 23]. Available from: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

Table 44.8 • Adverse Effects of Integrase Inhibitors

Drug Name (Alias)	Adverse Effects
Raltegravir (RAL)	Nausea, headache, diarrhea, fever, increased creatine kinase
Elvitegravir (EVG) (only available coformulated with cobi/TDF/FTC)	Nausea, diarrhea, hyperlipidemia
Dolutegravir (DTG)	Hypersensitivity reactions, including rash, constitutional symptoms, and organ dysfunction (eg, liver injury); insomnia; headache

Abbreviations: cobi, cobicistat; FTC, emtricitabine; TDF, tenofovir disaproxil fumarate.

evident. Its benefit for reducing HIV-related illness and death has been clearly established.

An independent association between cumulative exposure to replicating virus over time and death has also been observed. Thus, although ART is beneficial even when started later in the course of HIV disease, experts are finding that the damage done by unchecked replication early in the HIV disease course may be irreparable. Furthermore, the public health benefit of ART has been recognized and the concept of "treatment as prevention" has been fully accepted as an important attribute of ART. A recent landmark study, HPTN 052, involving nearly 2,000 HIV-serodiscordant couples with CD4 counts of 350 to 550 cells/mcL showed the benefit of early ART with a relative reduction of 96% in HIV-1 transmission to uninfected partners compared with delayed ART. Thus, ART is now recommended for all HIV-infected persons to both reduce the risk of disease progression and prevent HIV transmission.

KEY FACT

✓ ART is recommended for all HIV-infected persons to reduce risk of disease progression and to prevent HIV transmission

Recommended First-Line Antiretroviral Regimens

Many excellent options are available to patients with a new diagnosis of HIV infection. Selection should be guided by resistance test results, toxicity, pill burden, drug-drug interactions, and comorbid conditions. Initial treatment for ART-naïve patients involves 2 nucleoside analogue reverse transcriptase inhibitors, and a third drug from one of the following classes: integrase inhibitor, nonnucleoside analogue reverse transcriptase inhibitor, or protease inhibitor with a pharmacologic booster (cobicistat or ritonavir). Regimens classified as recommended for antiretroviral-naïve patients are therapies that have shown optimal and durable virologic efficacy in randomized controlled trials, are easy to use, and have favorable tolerability and toxicity profiles. Current

Box 44.5 • Initial Antiretroviral Therapy Regimens

Raltegravir plus tenofovir[a] and emtricitabine
Elvitegravir, cobicistat, tenofovir, and emtricitabine
Dolutegravir, abacavir, and lamivudine[b]
Dolutegravir plus tenofovir and emtricitabine

[a] Tenofovir can be given either as tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF).

[b] Abacavir can be used only for patients who are HLA-B*5701 negative.

recommended initial ART regimens for most patients are listed in Box 44.5.

Pre-exposure Prophylaxis

An important prevention tool that should be considered for all patients at high risk of acquiring HIV infection is pre-exposure prophylaxis (PrEP). PrEP is the use of antiretroviral drugs in HIV-negative patients who are at high risk for acquiring HIV infection. A fixed-dose formulation of tenofovir and emtricitabine is the only product currently approved for PrEP. Multiple randomized, placebo-controlled trials have shown that PrEP is more than 90% effective for preventing acquisition of HIV among persons who take the medication consistently. PrEP has been found to be effective for high-risk patients, including the following:

- Men or transgender women who are not in a mutually monogamous relationship and have sex with men
- Persons with an HIV-infected partner
- Persons who have sex with partners at high risk for HIV infection
- Injection drug users who have shared needles or other drug-injection equipment or who have been in a drug treatment program within the past 6 months

Assessing patients for their risk of acquiring HIV infection requires comfort and skill at obtaining a sexual and social history that includes illicit drug use. This skill is important for all clinicians caring for persons who may be candidates for PrEP.

Before prescribing PrEP, the clinician needs to confirm that a patient is at high risk for acquiring HIV infection and is currently negative for HIV. A serum HIV screening is required within a week before initiation of PrEP. Renal function needs to be assessed; an estimated creatinine clearance of more than 60 mL/min is required for PrEP because of potential for renal toxicity with tenofovir. Hepatitis B immune status needs to be assessed, and all persons susceptible to hepatitis B infection need to be vaccinated. Patients infected with hepatitis B need additional evaluation and can have reactivated infection if PrEP is interrupted. All persons considered for PrEP need risk-reduction counseling and services to minimize the risk of exposure to HIV infection.

Patients receiving PrEP need a clinical assessment at least every 3 months, and PrEP should be prescribed for no longer than 90 days. Renal function should be assessed 3 months after initiating PrEP; if stable, it is monitored every 6 months. PrEP should be discontinued if creatinine clearance decreases to less than 60 mL/min. Patients receiving PrEP require an HIV test, symptom screening for acute HIV infection, and clinical assessment every 3 months to assess tolerance for the medication. Pregnancy testing is required every 3 months, and it is required before PrEP is started in women with the potential for pregnancy. Sexually transmitted infection screening should be done every 3 to 6 months depending on the clinician's assessment of a patient's risk. The risk for acquiring HIV infection should be assessed at each visit, and each visit should be used to reemphasize risk reduction measures. The CDC guideline on PrEP should be reviewed, understood, and followed when prescribing PrEP.

KEY FACTS

✓ PrEP is effective for preventing HIV transmission through sex or from injection drug use if the at-risk person is compliant with treatment and does not miss doses

✓ Patients receiving PrEP need to be examined and screened for HIV at least every 90 days

✓ PrEP is recommended only for patients at high risk of acquiring HIV

Recommendations for Postexposure Prophylaxis

The risk of HIV infection after exposure is a function of the type of exposure and the infectivity of the exposure source. Infectivity is related to viral load. A person with an undetectable viral load is highly unlikely to transmit HIV. Exposure to a hollow needle, a deep puncture wound, or an exposure with visible blood on the device or needle is considered a high-risk exposure in the health care setting. Receptive anal intercourse with a partner known to have HIV infection and a high viral load is a high-risk sexual exposure.

Whenever possible, the HIV status of the exposure-source patient should be determined; the use of rapid HIV testing of source patients in such cases facilitates timely decision making. However, administration of postexposure prophylaxis (PEP) should not be delayed while waiting for test results.

In source patients who have tested negative for HIV infection, additional investigation to determine whether a source patient might be in the window period (the period during which the patient can be infected but has negative results of screening tests) is unnecessary unless the acute retroviral syndrome is clinically suspected. If the source patient is found to be HIV negative, PEP should be discontinued, and no follow-up HIV testing for this exposure is indicated.

PEP medication regimens should be started as soon as possible after occupational and high-risk sexual exposure to HIV and should be continued for 4 weeks.

The severity of exposure is no longer a criterion to determine the number of drugs to offer in an HIV PEP regimen; a regimen containing at least 3 antiretroviral drugs is now recommended routinely for all PEP. The preferred HIV PEP regimen is a combination of raltegravir or dolutegravir plus fixed-dose tenofovir disoproxil fumarate-emtricitabine at standard doses.

Follow-up of the exposed patient includes counseling; baseline and follow-up HIV testing; and monitoring for drug toxicity. Follow-up HIV testing is typically concluded at 6 months after an HIV exposure. However, if the newer fourth-generation HIV p24 antigen/HIV antibody combination test is used for follow-up HIV testing, the HIV testing may be concluded at 4 months after exposure.

KEY FACTS

- ✓ PEP medication regimens should be started as soon as possible after occupational or sexual exposure to HIV and should continue for 4 weeks
- ✓ A regimen of at least 3 antiretroviral drugs is recommended routinely for all PEP treatment
- ✓ The preferred HIV PEP regimen is a combination of raltegravir or dolutegravir plus fixed-dose tenofovir disaproxil fumarate-emtricitabine at standard doses for 28 days

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Immunocompromised Hosts

ELENA BEAM, MD; PRITISH K. TOSH, MD; M. RIZWAN SOHAIL, MD

Infections in immunocompromised patients may occur in the clinical setting of neutropenia, B-cell and T-cell deficiencies, immunoglobulin deficiencies, complement deficiencies, and leukocyte dysfunction. Some patients have multiple defects due to both the underlying disease and its treatment.

Febrile Neutropenia

Patients with neutropenia are at higher risk for infections with *Pseudomonas* species, gram-positive cocci, *Enterobacteriaceae*, and *Candida* and *Aspergillus* species. Patients who have neutropenia from the cytotoxic effects of chemotherapy, which breach normal mucosal and cutaneous barriers, are at the highest risk for infection. Fever in a patient with an absolute neutrophil count less than 0.5×10^9/L is usually due to translocation of bacteria from impaired mucosal surfaces in the oral cavity (oral mucosa and gingival crevices are rich sites of aerobic and anaerobic streptococci) and the lower gastrointestinal tract (contains gram-negative organisms and anaerobes). Bacteremia occurs in about 20% of neutropenic fever episodes, although in a majority of cases a clear pathogen is not established. With prolonged neutropenia, invasive mold disease may occur. Because of the high risk of morbidity, patients with acute leukemia who are expected to have prolonged neutropenia may be given antimicrobial prophylaxis with levofloxacin or a third-generation cephalosporin and a mold-active azole (posaconazole, voriconazole, or isavuconazole) during the neutropenia period. Acyclovir or valacyclovir is used for patients who are seropositive for herpes simplex virus or varicella zoster virus and receiving chemotherapy at the time of neutropenia.

Because morbidity and mortality rates are high for patients presenting with febrile neutropenia, empirical antimicrobial therapy should be started urgently. Empirical antimicrobial therapy should have activity against viridans group streptococci and gram-negative bacilli, including *Pseudomonas aeruginosa*. Hospitalization is recommended for high-risk patients, including those whose duration of neutropenia is expected to be longer than 7 days, or those with severe absolute neutropenia, localizing symptoms, intravascular catheter infection, hemodynamic instability, comorbidities, new oxygen requirement or presence of pulmonary infiltrate, or uncontrolled malignancy. Patients receiving fluoroquinolone prophylaxis should not be managed with empirical oral antibiotic therapy. Patients who are not at high risk can be managed as outpatients with close follow-up and first-line oral antimicrobial therapy (a combination of ciprofloxacin and amoxicillin-clavulanate empirically). The Multinational Association for Supportive Care in Cancer risk index score is a validated scoring method that can be used to help determine whether a patient meets the low- or high-risk category.

Recommended empirical regimens for hospitalized patients with neutropenic fever include monotherapy with an antipseudomonal cephalosporin such as cefepime, or piperacillin-tazobactam, or an antipseudomonal carbapenem such as meropenem. Vancomycin is not needed as a standard part of a neutropenic fever regimen. However, vancomycin should be added to the empirical regimen when a patient has evidence of pneumonia or severe mucositis, when ceftazidime is used as empirical therapy because of potential resistant viridans group streptococcal infection, when there is concern for central line infection or for skin or soft tissue infection, when a patient is known to have colonization with methicillin-resistant *Staphylococcus aureus*, or when hemodynamic instability is present. Empirical vancomycin therapy can be subsequently discontinued in this clinical setting if cultures are negative for methicillin-resistant *S aureus* or another resistant gram-positive organism.

Oral ulcerations and odynophagia are common in herpes simplex virus infection. The presence of ulcerating papules of ecthyma gangrenosum should suggest disseminated infections due to *Pseudomonas* or other gram-negative bacteria, and these organisms may be able to be cultured from the exudate or the blood. Bloodstream infection with gram-positive organisms (eg, *S aureus*, coagulase-negative staphylococci, enterococci, viridans group streptococci, *Corynebacterium jeikeium*) is often due to infected central venous catheters. *Streptococcus mitis* bacteremia may occur in mucositis and can be associated with septic shock and acute respiratory distress syndrome, especially in patients with leukemia, in whom there is increasing concern for development of resistance because of the widespread use of fluoroquinolones as prophylaxis for neutropenia.

Bacteremia due to anaerobic organisms is uncommon but should be considered in cases of perirectal abscess, gingivitis, or neutropenic enterocolitis (typhlitis). Persistent fever and abdominal symptoms in a person with neutropenia should raise this consideration. Anaerobic coverage should be added in these clinical settings.

Disseminated fungal infections often develop during prolonged cumulative neutropenia. The development of fever and an increased alkaline phosphatase level during recovery from neutropenia and the finding of microabscesses in the liver and spleen on computed tomography suggest the presence of hepatosplenic candidiasis. This condition requires months of antifungal therapy, usually with fluconazole. However, this particular complication is rare because of widespread use of prophylactic antifungal therapy in high-risk neutropenic patients. Nodular or consolidative pulmonary infiltrates in the clinical setting of prolonged antibacterial use and neutropenia suggest invasive aspergillosis. Affected patients may have an air crescent sign on computed tomography of the chest, and the diagnosis can be confirmed with a respiratory or tissue specimen or a positive result on an *Aspergillus* galactomannan assay of serum or bronchoalveolar lavage fluid. β-D glucan, a cell wall component of many fungal organisms, is an alternative serum marker of invasive fungal disease, although it is not specific for *Aspergillus* infections and may be positive in invasive *Candida* infections, *Pneumocystis* pneumonia, and *Pseudomonas* infections.

Antimicrobial agents active against *Aspergillus* include voriconazole, posaconazole, isavuconazole, amphotericin B, and the echinocandins, such as caspofungin. The presence of facial numbness, pain, or sinus disease in a patient with prolonged neutropenia raises suspicion for invasive fungal infection, including invasive mucormycosis (due most often to *Rhizopus* or *Mucor* species) and invasive aspergillosis. This clinical situation is a medical emergency and requires rapid diagnosis. Optimal treatment of rhinocerebral mucormycosis includes prompt surgical débridement and intravenous liposomal amphotericin compounds pending identification of the involved organism.

KEY FACTS

- ✓ Because of high morbidity and mortality rates in febrile neutropenia, empirical antimicrobial therapy should begin urgently. It should be effective against viridans group streptococci and gram-negative bacilli, including *P aeruginosa*
- ✓ Recommended empirical regimens include monotherapy with cefepime, piperacillin-tazobactam, or an antipseudomonal carbapenem, such as meropenem
- ✓ Vancomycin should be added to the empirical regimen when evidence of pneumonia or severe mucositis is present; concern exists for central line infection, or skin or soft tissue infection or when colonization with methicillin-resistant *S aureus* is found

Infections in Transplant Recipients

Recipients of hematopoietic stem-cell transplants receive conditioning chemotherapy that often leads to prolonged neutropenia and mucositis in the early transplant period before engraftment. These patients have complications similar to those with febrile neutropenia. In addition, patients who receive allogeneic transplants are at risk for graft-vs-host disease augmenting the degree of immunosuppression.

In solid organ transplant recipients, the risk of specific infection can be classified according to the posttransplant time course and the serologic status of recipient and donor for certain infections (eg, cytomegalovirus [CMV], toxoplasmosis). Most infections in the first month after transplant receipt are common nosocomial infections, such as wound infections, urinary tract infections, and central venous line infections. Donor-derived infections tend to present in the early posttransplant period, but they should remain in the differential diagnosis at later time courses. CMV, a common infection after transplant, can present with viremia or invasive disease, including fever, flulike symptoms, cytopenias, hepatitis, colitis, gastritis, retinitis, myocarditis, and pneumonitis. CMV-seronegative recipients of organs from a seropositive donor are at highest risk for CMV disease, and prophylactic antiviral agents are given for a predetermined duration. Most commonly valganciclovir is used to prevent infection during highest risk periods. The time of occurrence of opportunistic infections after solid organ transplant is summarized in Table 45.1. Pathogens associated with various immunodeficiency states are listed in Table 45.2.

Table 45.1 • Opportunistic Infections in Solid Organ Transplant

Month	Type of Infection After Transplant
1	Bacterial infections (related to wound, surgical site, venous lines, urinary tract), herpes simplex virus, hepatitis B virus
1-4	Cytomegalovirus, *Pneumocystis carinii, Listeria monocytogenes, Mycobacterium tuberculosis, Aspergillus, Nocardia, Toxoplasma*, hepatitis B virus, *Legionella*
2-6	Epstein-Barr virus, varicella-zoster virus, hepatitis C virus, *Legionella*
>6	*Cryptococcus neoformans, Legionella*

KEY FACTS

- ✓ CMV is a common infection after transplant that can present with fever, viremia, hepatitis, colitis, gastritis, retinitis, myocarditis, and pneumonitis
- ✓ CMV-seronegative recipients of organs from a CMV-seropositive donor are at highest risk for disease

Immunosuppressive Medications

Commonly used immunosuppressive agents, such as cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, and azathioprine, often given in combination with corticosteroids, are associated with several T-cell–mediated opportunistic infections. These include *Pneumocystis jiroveci* pneumonia, nocardiosis (pulmonary, brain, and cutaneous), histoplasmosis, cryptococcosis, coccidioidomycosis, listeriosis, CMV, varicella-zoster virus, and herpes simplex virus (Table 45.2).

The tumor necrosis factor-α inhibitors infliximab, adalimumab, and etanercept are associated with impaired granuloma formation and infections due to mycobacteria and endemic fungi such as *Histoplasma*, which can present as a disseminated infection.

Rituximab, an anti-CD20 chimeric monoclonal antibody, is used to treat many lymphoproliferative and rheumatic disorders and microscopic polyangiitis and granulomatosis with polyangiitis and other vasculitides. It is associated with the potential for fulminant hepatitis B reactivation. All patients should be screened for hepatitis B before rituximab use. In addition, progressive multifocal leukoencephalopathy, various viral infections, and reactivation can occur after rituximab use. Notably, B-cell depletion effects last for at least 6 months, and levels return to normal at around 12 months.

Natalizumab, an agent used for treatment of multiple sclerosis and Crohn disease, is associated with the development of progressive multifocal leukoencephalopathy.

Table 45.2 • Pathogens Associated With Immunodeficiency

Immunodeficiency	Usual Conditions	Pathogens
Neutropenia ($<0.5\times10^9$/L)	Cancer chemotherapy, adverse drug reaction, leukemia	Bacteria: Aerobic gram-negative bacilli (coliforms and *Pseudomonas, Staphylococcus aureus,* and viridans group streptococci) Fungi: *Aspergillus, Candida* species, *Mucormycosis*
Cell-mediated immunity	Solid organ transplant, HIV infection/AIDS, lymphoma (especially Hodgkin disease), corticosteroid therapy	Bacteria: *Listeria, Salmonella, Nocardia, Mycobacterium (Mycobacterium tuberculosis* and *Mycobacterium avium), Legionella* Viruses: CMV, HSV, VZV, JC virus Parasites: *Toxoplasma, Strongyloides stercoralis, Cryptosporidium* Fungi: *Candida, Cryptococcus, Histoplasma, Coccidioides, Pneumocystis jiroveci* (formerly *Pneumocystis carinii*)
Hypogammaglobulinemia or dysgammaglobulinemia	Multiple myeloma, congenital or acquired deficiency, chronic lymphocytic leukemia	Bacteria: *Streptococcus pneumoniae, Haemophilus influenzae* type B Parasites: *Giardia* Viruses: enteroviruses
Complement deficiencies C2, 3 C5 C6-8	Congenital	Bacteria: *S pneumoniae, H influenzae, S aureus*, Enterobacteriaceae
Alternative pathway		*Neisseria meningitidis, S pneumoniae, H influenzae, Salmonella*
Hyposplenism	Splenectomy, hemolytic anemia	*S pneumoniae, H influenzae, Capnocytophaga canimorsus*
Defective chemotaxis	Diabetes mellitus, alcoholism, renal failure, lazy leukocyte syndrome, trauma, SLE	Bacteria: *S aureus*, streptococci Fungi: *Candida, Aspergillus, Mucormycosis*
Defective neutrophilic killing	Chronic granulomatous disease, myeloperoxidase deficiency	Catalase-positive bacteria: *S aureus, Escherichia coli, Candida* species

Abbreviations: CMV, cytomegalovirus; HSV, herpes simplex virus; SLE, systemic lupus erythematosus; VZV, varicella-zoster virus.

From Bartlett JG. 1998 Pocket book of infectious disease therapy. 9th ed. Baltimore (MD): Williams & Wilkins; c1998. p. 236; used with permission.

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Microorganism-Specific Syndromes

ELENA BEAM, MD; PRITISH K. TOSH, MD; M. RIZWAN SOHAIL, MD

There are several human pathogens for which the microorganism is, in many ways, synonymous with the syndrome it causes. This chapter briefly reviews the microbiology, associated clinical syndromes, testing, and treatment for some of the most clinically significant pathogens, grouped by organism type.

Bacteria

Actinomycetes

Actinomyces israelii, an anaerobic, gram-positive, branching, filamentous organism, is the most common cause of human actinomycosis and is part of the normal oral flora. Infections are associated with any condition that creates an anaerobic environment (such as trauma with tissue necrosis). The pathologic characteristic is formation of so-called sulfur granules, which are clumps of filaments.

Perimandibular actinomycosis is characterized by a chronic draining sinus condition and may follow a dental extraction. Pulmonary actinomycosis develops when aspirated material reaches an area of lung with decreased oxygenation and often occurs in association with poor dental hygiene. A chronic suppurative pneumonitis may develop and eventually result in a sinus tract draining through the chest wall. *Actinomyces* organisms also may be found in cultures of tubo-ovarian abscesses and other pelvic infections. They are especially associated with pelvic inflammatory disease developing in a woman with an intrauterine device.

Bartonella Species

Bartonella henselae, Bartonella bacilliformis, and *Bartonella quintana* are the most common *Bartonella* species that cause human disease. Bartonellae are gram-negative bacteria that are commonly transmitted by various arthropods, such as lice, ticks, and fleas. *Bartonella henselae* is the primary causative agent of cat-scratch disease. This disease is characterized by a papule or pustule at the site of inoculation, followed by tender enlargement of the regional lymph nodes, with or without low-grade fever and malaise. Exposure to domestic cats (especially kittens) is the main risk factor. About 10% of patients with cat-scratch disease have extranodal manifestations.

Infection with the *Bartonella* species, particularly *B quintana* and *B henselae,* can disseminate in patients with HIV infection or AIDS or in other immunocompromised patients. Disseminated infection can present with cutaneous and visceral involvement, particularly of the liver. *Bartonella henselae* acquisition is associated with cat exposure, and *B quintana* occurs more often in alcoholic, homeless persons without specific cat exposure. *Bartonella quintana* can be transmitted by the bite of infected cat fleas and is the pathogen responsible for the classic presentation of trench fever. *Bartonella* infection may cause ocular involvement, is one of the causes of parinaud oculoglandular syndrome, and can present as neuroretinitis in up to 2% of cases of cat-scratch disease.

Diagnosis of cat-scratch disease is based on clinical presentation and serologic evidence of antibodies to *B henselae* or other *Bartonella* species. In tissue biopsy specimens, the organisms can be seen with Warthin-Starry stain. Although cat-scratch disease may be self-limiting, antibiotics are generally recommended. Antibiotics have been shown to improve resolution of lymphadenopathy. Azithromycin is the most effective antibiotic for treatment of bartonellosis.

Bartonella is one of the most common pathogens recognized as a cause of culture-negative endocarditis, although prevalence varies substantially with geographic location. Management of *Bartonella* endocarditis involves combination antimicrobial therapy, including doxycycline as an active part of the regimen.

Brucella

Most cases of brucellosis acquired in the United States occur in Texas, California, Virginia, and Florida. Although rare in the

United States (100-200 cases per year), brucellosis may occur in meat handlers, persons exposed to livestock, or persons who consume unpasteurized dairy products. Brucellosis should be suspected in recent immigrants with fever or travelers who become ill after returning from developing countries. Personnel in microbiology laboratories should be warned when specimens from patients suspected of having brucellosis are sent for processing as a means to allow special precautions to be taken. Brucellosis may cause a chronic granulomatous disease with caseating granulomas. Serologic testing, extended-incubation blood cultures, and bone marrow cultures are helpful for making the diagnosis. Blood culture results are usually positive in acute brucellosis. Treatment is with doxycycline in combination with either streptomycin or rifampin. Endocarditis due to brucellosis is managed with a combination of antimicrobials and a surgical approach.

Clostridium botulinum

Clostridium botulinum produces a heat-labile neurotoxin that inhibits acetylcholine release from cholinergic terminals at the motor end plate. Botulism usually is caused by the ingestion of preformed botulinum toxin contained in contaminated food (eg, home-canned products, improperly prepared or handled commercial foods). Wound botulism results from contaminated traumatic injury. Infant botulism can result from gastrointestinal proliferation of *C botulinum* after ingestion of a food containing the toxin-producing organism (eg, honey).

The clinical symptoms of botulism include cranial nerve palsies (eg, diplopia) with progression to dysphagia and dyspnea, followed by descending flaccid paralysis with normal sensation. Patients are usually alert and oriented and have intact deep tendon reflexes. Fever is rare.

Treatment of botulism is primarily supportive. A heptavalent equine antitoxin is available and has been shown to prevent progression of the disease. Antibiotic therapy should not be used for infant botulism because the lysed organisms will release more botulinum toxin.

Clostridium tetani

Clostridium tetani is a strictly anaerobic, gram-positive rod that produces a neurotoxin responsible for the clinical manifestations of tetanus. Although tetanus is rare in the United States, 200 to 300 cases still occur annually, mostly in elderly persons who have never been immunized.

The first muscles affected by tetanus are controlled by cranial nerves, resulting in trismus (ie, lockjaw). As the disease progresses, other muscles become involved (shown through generalized rigidity, spasms, and opisthotonos). Sympathetic overactivity (labile hypertension, hyperpyrexia, and arrhythmias) is common. The diagnosis of tetanus is based on clinical findings, although a characteristic electromyogram is suggestive of the disease.

Treatment of tetanus includes supportive care, proper wound management, and administration of antiserum (human tetanus immune globulin). Penicillin G or metronidazole should be administered to eradicate vegetative organisms in the wound. Clinical tetanus does not induce adequate protective immunity, and patients should receive a primary vaccine series after recovery from the illness.

Corynebacterium diphtheriae

Diphtheria is a classic infectious disease that is highly contagious, but it is easily preventable with vaccination. Diphtheria causes a focal *Corynebacterium diphtheriae* infection of the respiratory tract (pharynx [60%-70%], larynx, nasal passages, or tracheobronchial tree). A tightly adherent, gray pseudomembrane is the hallmark of diphtheria, but disease can occur without pseudomembrane formation. Manifestations depend on the extent of the upper airway involvement and the presence or absence of systemic complications due to toxin. Toxin-mediated complications include myocarditis (10%-25%), which causes congestive heart failure and arrhythmias, and polyneuritis (5%) (bulbar dysfunction followed by peripheral neuropathy). Respiratory muscles may be paralyzed.

The diagnosis of diphtheria is definitively established by culture with Löffler medium. Equine antiserum is the main therapy. Although there is no evidence that antimicrobial agents alter the course of disease, they may prevent transmission to susceptible hosts. Erythromycin and penicillin G are active against *C diphtheriae*. Nonimmune persons exposed to diphtheria should be evaluated and receive treatment with erythromycin or penicillin G if culture results are positive. They also should be immunized with diphtheria-tetanus toxoid.

Nocardia

Nocardia organisms are aerobic, gram-positive, filamentous, and branching and are visualized with a modified acid-fast stain (Figure 46.1). Infections are most often opportunistic and occur in immunosuppressed patients, including those with HIV infection or AIDS. Nevertheless, *Nocardia* infections can occur in healthy persons also, primarily from trauma and direct inoculation of the organism.

The respiratory tract is the usual portal of entry for *Nocardia* infection. Chronic pneumonitis and lung abscess are the most common findings. Hematogenous spread to the brain is relatively common. Computed tomography or magnetic resonance imaging of the head is advised in immunocompromised patients with pulmonary nocardiosis.

Diagnosis depends on appropriate stains and cultures (the organism grows on fungal media). Because sputum culture is relatively insensitive, specimens obtained by bronchoscopy or open lung biopsy may be needed to confirm the diagnosis. The disease must be differentiated from other causes of chronic pneumonia (such as bacterial, actinomycotic, tubercular, and fungal infections).

Therapy involves drainage of abscesses and high doses of sulfonamide drugs (trimethoprim-sulfamethoxazole is the drug of choice), although some species of *Nocardia* show evidence

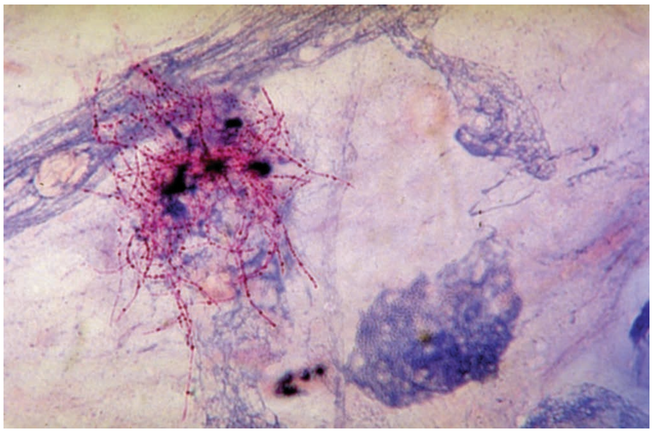

Figure 46.1. Nocardia asteroides *(Modified Acid-Fast Stain, Original Magnification ×450).*

of sulfonamide resistance. Other antimicrobial agents used for nocardiosis include imipenem, amikacin, minocycline, and cephalosporins. Severe disease is managed with combination antimicrobial therapy, particularly while awaiting the results of antimicrobial susceptibility testing. Duration is guided by clinical or radiographic response to therapy.

Spirochetes

Leptospirosis

Leptospira interrogans infection is acquired by contact with urine from infected animals (eg, rats, dogs) and should be considered in the differential diagnosis of febrile travelers who were exposed to freshwater. *Leptospira* infection causes a biphasic illness. The first phase, the leptospiremic phase, is characterized by abrupt-onset headache (98%), fever, chills, conjunctivitis, severe muscle aching, gastrointestinal tract symptoms (50%), changes in sensorium (25%), rash (7%), and hypotension. The presence of conjunctival suffusion is a clue to the diagnosis. This phase lasts 3 to 7 days. Improvement in symptoms coincides with disappearance of *Leptospira* organisms from blood and cerebrospinal fluid (CSF).

The second phase, the immune stage, occurs after a relatively asymptomatic period of 1 to 3 days, when fever and generalized symptoms recur. Meningeal symptoms often develop during this period. The second phase is characterized by the appearance of immunoglobulin (Ig) M antibodies. Most patients recover after 1 to 3 days. However, in serious cases, hepatic dysfunction and renal failure may develop, and the combination of jaundice and renal failure is referred to as Weil disease. Death in patients with leptospirosis usually occurs in the second phase as a result of hepatic and renal failure.

The diagnosis of leptospirosis is established on the basis of clinical presentation and of cultures of blood and, rarely, CSF in the first 7 to 10 days of infection. Urine culture results can remain positive in the second week of illness. Serologic testing has high specificity but low sensitivity, especially in the acute phase of disease, although it increases to 89% specificity and 63% sensitivity in the second phase. Serologic testing is most frequently used clinically to establish the diagnosis. Treatment with penicillin G is effective only when given within the first 5 days from onset of symptoms. Oral amoxicillin or doxycycline can be used for mild-to-moderate illness.

Lyme Disease

Epidemiologic Factors

Lyme disease is the most common vector-borne (*Ixodes* ticks) disease reported in the United States. The incidence of disease is highest in spring and summer, when exposure to ticks is most common. Ticks must be attached to the skin for more than 36 hours to transmit infection (ticks are engorged with blood on inspection). Although Lyme disease has been reported in most states, it is most common in coastal New England and New York State, the Mid-Atlantic states, Oregon, northern California, and the Upper Midwest. Coinfection with *Babesia* or *Anaplasma* may occur in up to 15% of cases and may increase symptom severity.

Clinical Syndromes

Stage 1 (early stage) occurs from 3 to 32 days after the tick bite. Erythema migrans (solitary or multiple lesions) is the hallmark of Lyme disease and occurs in 80% or more of infected persons. It can be associated with fever, lymphadenopathy, and meningismus. The rash of erythema migrans usually enlarges and resolves over 3 to 4 weeks. *Borrelia burgdorferi* disseminates hematogenously early in the course of the illness.

Stage 2 occurs weeks to months after untreated stage 1 disease. In 10% to 15% of cases, neurologic abnormalities develop (eg, facial nerve palsy, lymphocytic meningitis, encephalitis, chorea, myelitis, radiculitis, peripheral neuropathy). Carditis (reversible atrioventricular block) occurs in 5% to 10% of cases. Conduction abnormalities are mostly reversible, and permanent heart block is rare.

Stage 3, although uncommon, can develop months to years after the initial untreated infection. Monoarticular or oligoarticular arthritis occurs in 50% of patients at this stage and becomes chronic in 10% to 20%. Chronic arthritis is more common in those with HLA-DR2 and HLA-DR4. Almost all patients with stage 3 Lyme disease have detectable serum antibodies against *B burgdorferi*. Magnetic resonance imaging may show demyelination.

Diagnosis

Results of screening serologic testing may be negative in the acute stage (with the erythema migrans rash) of illness and, as such, is not recommended during this stage. Antibodies to *B burgdorferi* can be detected by enzyme-linked immunosorbent assay after the first 2 to 6 weeks of illness. Western blot test is used to confirm the diagnosis when the screening enzyme-linked immunosorbent assay result is positive. This

2-step test approach is both sensitive and specific for establishing the diagnosis of Lyme disease. Serologic tests should be ordered only in cases of a clinical syndrome compatible with Lyme disease. False-positive results may occur with infectious mononucleosis, rheumatoid arthritis, systemic lupus erythematosus, echovirus infection, and other spirochetal disease because of antibody cross-reactivity. According to evidence-based criteria of the Centers for Disease Control and Prevention, a Western blot result is positive when at least 2 IgM bands are detected (within the first few weeks of infection) or at least 5 IgG bands are detected after the first weeks. Alternative diagnostic tests are not supported by the evidence-based criteria. Antibodies can persist for years despite appropriate therapy, and follow-up serologic testing for treatment response is not recommended.

Treatment

Patients who reside in or visit endemic areas and have the characteristic skin lesion of erythema migrans should have treatment without any serologic testing. For stage 1 (early) Lyme disease in the absence of neurologic involvement or complete heart block, doxycycline (100 mg orally twice daily), amoxicillin (500 mg 3 times daily), and cefuroxime axetil (500 mg twice daily) are effective therapeutic agents. Recommended treatment duration is 14 days (range, 10-21 days).

In Lyme disease carditis, the outcome is usually favorable. For first- or second-degree atrioventricular block, infection should be treated with oral agents, whereas third-degree heart block should be treated with intravenous (IV) ceftriaxone (2 g daily) or IV penicillin G (20 million units daily) for 14 to 21 days. Lyme disease meningitis, radiculopathy, or encephalitis should be treated parenterally.

The outcome in patients with facial palsy in Lyme disease is also usually favorable. If only facial nerve palsy is present (no symptoms of meningitis or radiculoneuritis), oral therapy with doxycycline or amoxicillin is used.

If Lyme disease meningitis is present, ceftriaxone (2 g daily) or IV penicillin G (20 million units daily) should be administered for 14 to 28 days.

Optimal treatment regimens (oral vs IV) for Lyme disease arthritis are not established yet. Joint rest and repeated joint aspirations are often needed. Response to antibiotics may be delayed. If no neurologic disease is present, doxycycline is given (100 mg orally twice daily) for 28 days. An alternative regimen is amoxicillin and probenecid (500 mg each, 4 times daily) for 28 days or ceftriaxone (2 g IV daily) for 14 to 28 days. Synovectomy may be necessary in the management of persistent monoarticular Lyme disease arthritis that has not responded to antimicrobial therapy.

In patients who have persistence of nonspecific symptoms despite appropriate antimicrobial therapy for Lyme disease, post-Lyme syndrome may be diagnosed. These patients, however, do not benefit from additional antimicrobial courses.

KEY FACTS

- ✓ For Lyme disease, ticks must be attached to the skin for more than 36 hours to transmit infection
- ✓ Lyme disease is most common in coastal New England states and New York State, the Mid-Atlantic states, Oregon, northern California, and the Upper Midwest
- ✓ Coinfection with *Babesia* or *Anaplasma* may occur in up to 15% of cases and may increase symptom severity
- ✓ Stage 1 Lyme disease occurs at 3 to 32 days after the tick bite
- ✓ Erythema migrans in solitary or multiple lesions is the hallmark of Lyme disease and occurs in 80% or more of cases

Rickettsiae

All rickettsial infections are transmitted by an arthropod vector. Most are associated with a rash, except ehrlichiosis.

Rickettsia rickettsii infection (Rocky Mountain spotted fever [RMSF]) is associated with a rash that may be indistinguishable from that of meningococcemia. RMSF rash begins on the extremities and moves centrally. RMSF is most common in the Mid-Atlantic states and Oklahoma, not the Rocky Mountain states. Doxycycline is the treatment of choice.

Ehrlichia species are gram-negative intracellular bacteria that resemble rickettsial organisms and preferentially infect lymphocytes, monocytes, and neutrophils. *Ehrlichia chaffeensis* infects monocytes (also called *human monocytic ehrlichiosis*), and *Ehrlichia equi* and *Anaplasma phagocytophilum* infect neutrophils (also called *human granulocytic ehrlichiosis* or *anaplasmosis*). Ehrlichiosis is seasonal; peak incidence occurs in summer. The vectors are the common dog tick (*Dermacentor variabilis*) and the lone star tick (*Amblyomma americanum*) for *E chaffeensis* and the deer tick (*Ixodes scapularis*; the same vector as in Lyme disease) for the agent of anaplasmosis. The incubation period is short (average, 7 days), and patients present with acute-onset fever, chills, malaise, headache, and myalgia. Fewer than 50% of patients with anaplasmosis have a rash. Rarely, a rash develops with human monocytic ehrlichiosis. Important laboratory features include leukopenia, thrombocytopenia, and increased levels of hepatic transaminases. Disease severity is variable, but severe complications, including death, can occur. Coinfection with *Babesia* and *B burgdorferi* (Lyme disease) can occur and can be especially severe. Identification of *Babesia* coinfection is of importance, given the need for alternative antibiotic therapy. Diagnosis is based on serologic testing (indirect immunofluorescent assay) or detection through polymerase chain reaction amplification. Treatment is with doxycycline for 7 to 10 days.

KEY FACTS

- ✓ RMSF is associated with a rash that can be indistinguishable from that of meningococcemia, beginning on the extremities and moving centrally
- ✓ RMSF is most common in the Mid-Atlantic states and Oklahoma
- ✓ Doxycycline for 7 to 10 days is the treatment of choice
- ✓ Important laboratory features of RMSF include leukopenia, thrombocytopenia, and increased levels of hepatic transaminases
- ✓ Diagnosis is based on indirect immunofluorescent assay or detection with polymerase chain reaction amplification

Coxiella burnetii

Coxiella burnetii infection, the cause of Q fever, is acquired by inhalation of contaminated aerosol particles of dust, earth, or feces or by exposure to animal products, especially infected placentas. Cattle and sheep are common sources, but other animals (usually asymptomatic), including cats, can harbor the disease. An isolated febrile illness is the most common disease manifestation, and most such cases present with pneumonitis. Granulomatous hepatitis occurs in 15% of cases. Endocarditis (1%) and central nervous system (CNS) manifestations are rare. Q fever is one of the causes of culture-negative endocarditis. It usually is diagnosed with serologic testing. Acute Q-fever pneumonitis or hepatitis is treated with doxycycline or a fluoroquinolone for 2 weeks. Endocarditis typically requires combination, and prolonged (>18 months), therapy.

Fungi

Coccidioidomycosis

Coccidioides immitis is endemic in the southwestern United States, especially the San Joaquin Valley of California and central Arizona, and in Mexico. Disseminated disease is most likely to occur in men (especially Filipino and black men), pregnant women, and immunocompromised persons, including HIV-infected patients, regardless of sex.

Most primary infections with *C immitis* are subclinical. The most common clinical manifestation is self-limited pneumonitis. Common manifestations are dry cough and fever (called *valley fever*) that may resemble influenza. Associated findings include hilar adenopathy, pleural effusion (12%), thin-walled cavities (5%), and solid "coin" lesions. Disseminated infection predominantly affects the CNS, skin, bones, and joints. In immunocompetent hosts, a history of coccidioidomycosis infection is thought to provide immunity against future infections.

The diagnosis of coccidioidomycosis is primarily based on detecting the organism through culture or biopsy with silver stains. A *C immitis* serologic titer greater than 1:4 is suggestive of infection (≥1:16 indicates likely disseminated infection). The diagnosis of coccidioidomycosis meningitis is usually established by detecting CSF antibodies. A biopsy specimen may show the diagnostic *C immitis* spherule (Figure 46.2). Laboratory abnormalities may include eosinophilia and hypercalcemia. Coccidioidomycosis is one of the infectious triggers of erythema nodosum.

Fluconazole, itraconazole, and amphotericin B are effective agents for treating coccidioidomycosis. The acute pulmonary form is usually self-limited, and observation may be adequate. However, therapy is indicated when a patient is pregnant, is immunocompromised, or has worsening infection without therapy. Amphotericin B is the drug of choice for severe manifestations and for pregnant women with coccidioidomycosis. An alternative to fluconazole is itraconazole, although itraconazole requires close therapeutic drug monitoring and treatment may be complicated by poor absorption. For meningitis, therapy with high-dose fluconazole is preferred and has largely replaced intrathecal amphotericin B. Because of the high relapse rate of *C immitis* meningitis, long-term suppressive therapy is recommended, usually with fluconazole. Given their risk for teratogenicity, azole antifungals such as fluconazole should be avoided during the first trimester of pregnancy.

Histoplasmosis

Histoplasma capsulatum is a dimorphic fungus that grows as a small yeast in tissues and as a mold at room temperature.

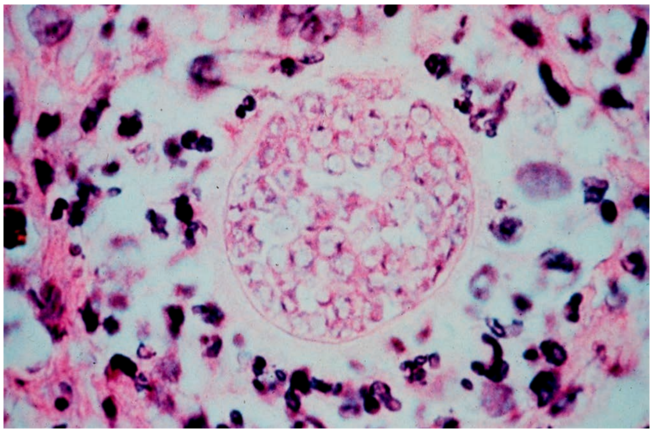

Figure 46.2. Coccidioides immitis *Spherules in a Clinical Specimen (Grocott Methenamine-Silver Stain).*

Although present in many areas of the world, histoplasmosis is especially prevalent in the Ohio, Missouri, and Mississippi river valleys and parts of Mexico and Central America. Outbreaks have been associated with large construction projects and exposure to bird or bat droppings. Histoplasmosis is acquired by inhalation of spores, and the risk of acquisition is increased with certain activities, including cave diving and bridge or other construction. Although healthy individuals may acquire histoplasmosis, patients with AIDS or cell-mediated immune deficiency are particularly susceptible to disseminated disease. *H capsulatum* infection is one of the causes of caseating granulomata.

Primary (acute) histoplasmosis may be clinically indistinguishable from influenza or other upper respiratory tract infections. After resolution, multiple small, calcified granulomas may be seen on subsequent chest radiographs. The progressive (disseminated) form of histoplasmosis is uncommon but serious. The disseminated form and reactivation of prior disease are most likely to occur in infants, elderly men, and immunosuppressed persons, including those with HIV infection or AIDS and those receiving therapy with tumor necrosis factor-α inhibitors, such as etanercept and infliximab. Disseminated histoplasmosis typically involves the reticuloendothelial system—bone marrow, spleen, lymph nodes, and liver. Manifestations may resemble those of lymphoma, such as weight loss, fever, anemia, increased erythrocyte sedimentation rate, and splenomegaly. Bone marrow involvement may be associated with pancytopenia and hemophagocytic lymphohistiocytosis. Mucosal ulcers, which can occur throughout the gastrointestinal tract and mouth, are not infrequent. Chronic cavitary pulmonary disease due to *Histoplasma* infection may resemble tuberculosis and tends to occur in patients with preexistent pulmonary disease, such as chronic obstructive pulmonary disease.

Positive serologic findings are helpful for confirming the diagnosis of histoplasmosis, although the sensitivity may be decreased in immunosuppressed patients. Biopsy, silver stain, and cultures of infected tissues are the best means of establishing the diagnosis. Detection of *Histoplasma* antigen in urine, CSF, or serum is sensitive, especially for the diagnosis of disseminated disease and to follow up on treatment response.

The mild, acute forms of histoplasmosis in immunocompetent patients are usually self-limited and do not require therapy. Amphotericin B is the drug of choice for initial therapy for all severe, life-threatening cases. Itraconazole is effective for most nonmeningeal, non–life-threatening cases and to complete the treatment course of severe disease. Patients with AIDS require long-term maintenance therapy.

KEY FACTS

- ✓ Histoplasmosis is especially prevalent in Ohio, Missouri, and Mississippi river valleys and parts of Mexico and Central America
- ✓ Primary acute histoplasmosis may be indistinguishable from influenza or other upper respiratory tract infections. After its resolution, multiple small, calcified granulomas may be seen on chest radiographs
- ✓ Dissemination and reactivation of prior disease are most likely in infants, elderly men, and immunosuppressed persons, including those with HIV infection or AIDS or receiving tumor necrosis factor-α inhibitors
- ✓ Disseminated histoplasmosis typically involves bone marrow, spleen, lymph nodes, and liver
- ✓ Manifestations may resemble those of lymphoma, such as weight loss, fever, anemia, increased erythrocyte sedimentation rate, and splenomegaly. Bone marrow involvement may be associated with pancytopenia

Blastomycosis

Blastomyces dermatitidis is another dimorphic fungal pathogen. In tissue, the yeast has thick walls and broad-based buds (±10 mm in diameter) (Figure 46.3). In culture at room temperature, a mycelial form grows. Blastomycosis is endemic in the southeastern United States and the Upper Midwest. Primary pulmonary blastomycosis may be asymptomatic, but organisms may disseminate hematogenously to skin, bone (especially vertebrae), male genitalia (ie, prostate, epididymis, and testis), and the CNS. Granulomas occur, but calcification is less frequent than with histoplasmosis or tuberculosis. Like histoplasmosis, blastomycosis is a cause of chronic meningitis.

The pulmonary form has no characteristic findings. Pleural effusion is rare, hilar adenopathy develops occasionally, and cavitation is infrequent. It often mimics carcinoma of the lung. Cutaneous involvement with blastomycosis is common. Lesions, especially on the face, are characteristically painless and nonpruritic and have a sharp, spreading border. Chronic crusty lesions may occur.

The diagnosis of blastomycosis is based on results of biopsy, fungal stains, and cultures. Serologic testing can be helpful. Urine antigen is sensitive in disseminated disease, although testing may cross-react with other endemic fungi such as *Histoplasma*. Amphotericin B is reserved primarily for life-threatening

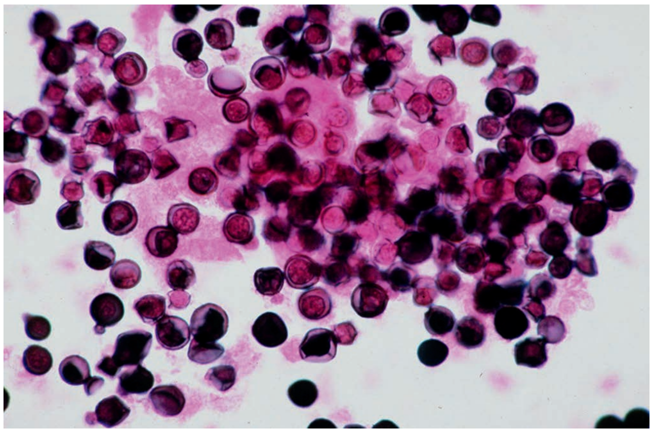

Figure 46.3. Blastomyces dermatitidis *in Bronchoalveolar Lavage (Silver Stain, Original Magnification ×450).*

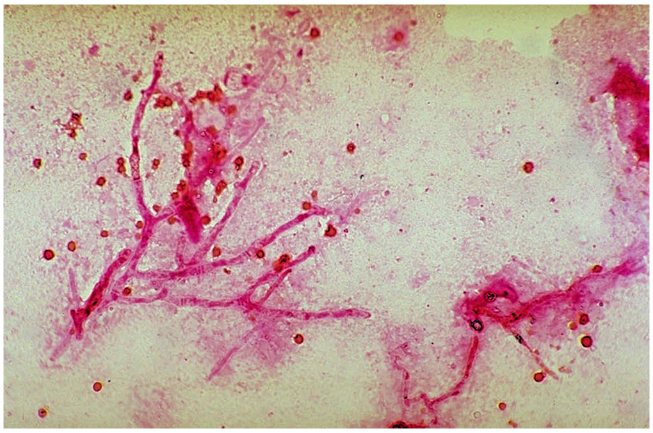

Figure 46.4. Aspergillus fumigatus *in Bronchoalveolar Lavage (Original Magnification ×450).*

infections. Mild-to-moderate nonmeningeal blastomycosis can be treated with itraconazole for 6 months.

Sporotrichosis

Sporothrix schenckii, another dimorphic fungal pathogen, is seen as round, cigar-shaped yeast in tissues, but culture at room temperature yields a mycelial form. *Sporothrix schenckii* is most often found in soil and plants. Sporotrichosis is usually transmitted through cutaneous inoculation (so-called rose gardener disease) and, rarely, through inhalation causing chronic pneumonitis (with cavitation and empyema).

Cutaneous sporotrichosis presents as characteristic crusty lesions with suppuration and granulomatous reaction. New lesions develop along the lymphatic system of the extremities from the initial site of infection (sporotrichoid spread). Similar lesions may be produced by infection with *Mycobacterium marinum* and *Nocardia* or by cutaneous leishmaniasis. Septic arthritis can occasionally occur.

The diagnosis of sporotrichosis may be difficult and depends on clinical recognition of the cutaneous lesions in most instances. Biopsy, fungal culture, and serologic testing can help establish the diagnosis.

For the cutaneous or lymphocutaneous form, itraconazole is the therapy of choice. An effective alternative is supersaturated solution of potassium iodide. Amphotericin B is recommended for disseminated disease (pulmonary and joint), although such disseminated disease may respond poorly to therapy.

Aspergillosis

Aspergillus is an opportunistic pathogen that causes infection in immunocompromised persons, particularly those with prolonged neutropenia. Although any *Aspergillus* species can cause disease, *Aspergillus fumigatus* is the most common pathogen. The organisms have large, septated hyphae branching at 45° angles (Figure 46.4). In contrast, Zygomycetes have aseptate, ribbonlike hyphae with wide-angle branching. In neutropenic persons, *Aspergillus* may invade blood vessels, producing a striking thrombotic angiitis. Metastatic foci may cause suppurative abscess formation.

The form of aspergillosis disease primarily is determined by the nature of the immunologic deficit in the infected person. Neutropenia predisposes to rapidly invasive bronchopulmonary disease with early dissemination to the brain and other tissues. The longer the duration of neutropenia, the higher the risk of invasive aspergillosis. Prompt therapy with a mold-active azole (eg, voriconazole, posaconazole, or isavuconazole) or large doses of amphotericin B and the resolution of neutropenia are necessary to control the disease. Diagnosis should be suspected when *Aspergillus* is isolated from any source in a susceptible person.

Aspergillus frequently colonizes the respiratory tract. Hence, isolating the organism from the sputum of an immunocompetent person usually does not indicate disease and does not require treatment.

However, *Aspergillus* may cause localized disease in persons with normal immunologic function. It may produce a "fungus ball" in preexisting lung bullae or cavities (eg, previous tuberculosis, emphysema). Hemoptysis is the main symptom. Surgical excision may be necessary to prevent lethal hemorrhage.

The symptoms of allergic bronchopulmonary aspergillosis resemble those of asthma. It is characterized by migratory pulmonary infiltrates; thick, brown, tenacious mucous plugs in the sputum; eosinophilia; and high titers of anti-*Aspergillus* antibodies. It typically occurs in the clinical setting of chronic asthma. Treatment primarily entails glucocorticoids, and the goal of antifungal therapy is to limit the overall corticosteroid requirement.

Cryptococcosis

Cryptococcus neoformans is a yeast in both tissue and culture. It is 4 to 7 mcm in diameter and has a characteristic narrow-based budding and a thick capsule (Figure 46.5). *Cryptococcus neoformans* is an opportunistic pathogen infecting persons with T-cell deficiency or dysfunction (eg, patients with Hodgkin

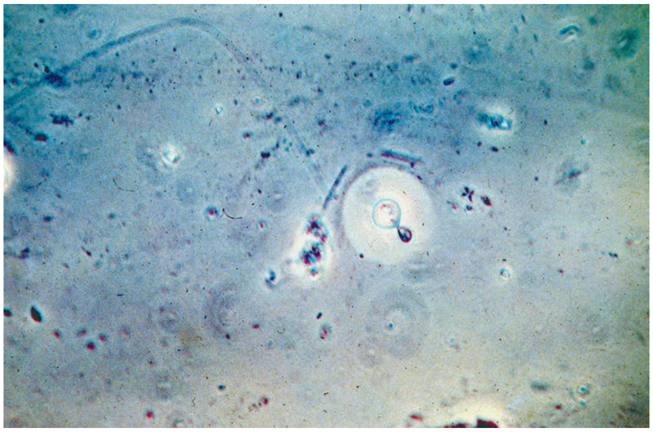

Figure 46.5. Cryptococcus neoformans *in Cerebrospinal Fluid (Original Magnification ×450).*

lymphoma, hematologic malignancy, organ transplant, exogenous corticosteroid therapy, chronic liver disease, AIDS, or idiopathic CD4 lymphopenia).

Cryptococcus neoformans is acquired by inhalation. From the lungs, it disseminates widely and easily crosses into the CNS. Pneumonia and meningitis are the most common forms of cryptococcosis. Meningitis may be insidious, with headache as the only symptom. Cranial nerve involvement may develop (including blindness with optic nerve involvement).

Cryptococcal infection can be diagnosed with fungal culture (eg, CSF, blood, sputum, urine) and silver stain of biopsy tissue. The cryptococcal antigen test is the most helpful of all fungal serologic tests; it detects capsular antigen, whereas most other fungal serologic tests measure antibody response. If *C neoformans* is isolated from any source (eg, sputum, urine, blood) in an immunosuppressed patient, a lumbar puncture should be done to rule out meningitis, even in the absence of symptoms.

Choice of therapy depends on the extent of disease and host immune function. Mild-to-moderate non-CNS cryptococcosis can be treated with fluconazole for 6 to 12 months. However, in cases of severe presentation, immunocompromised hosts, disseminated disease, and CNS involvement, treatment with IV amphotericin B in combination with flucytosine should be provided for 2 weeks, followed by fluconazole therapy for 6 to 12 months. Oral fluconazole therapy is continued indefinitely for patients with severe immunosuppression and poor immune reconstitution.

Cryptococcus gattii infection occurs primarily in the Pacific Northwest in the United States and is managed similarly to *C neoformans*.

Candidiasis

Candida is a normal part of human microflora. It grows as both yeast and hyphal forms simultaneously. Although *Candida albicans* is the most common species, numerous other species can cause human disease. *Candida* causes mucosal and cutaneous infections in both normal and immunocompromised persons. Invasive disease primarily occurs in neutropenic hosts and as a nosocomial bloodstream infection.

Examples of candidiasis in a healthy person include diaper rash and intertrigo, in which *Candida* growth on moist skin surfaces produces irritation with characteristic satellite lesions. Vulvovaginal candidiasis is common, especially in women after receiving antibiotic therapy for bacterial infection. Treatment with topical antifungal agents or a single dose of oral fluconazole is usually curative for *Candida* vaginitis. Diabetes mellitus, corticosteroid therapy, oral contraceptives, obesity, and HIV infection predispose to recurrent vulvovaginal candidiasis. Oral thrush may result from these same risk factors.

Candida species cause 5% to 10% of nosocomial bloodstream infections. Candidemia most often occurs in critically ill patients receiving broad-spectrum antibiotics and parenteral nutrition. Neutropenia is another predisposing factor. Current blood culture techniques usually detect *Candida*, but culture results may be delayed. All IV catheters should always be removed or replaced when bloodstream infection with *Candida* is discovered. Metastatic abscesses can occur in any site after an episode of candidemia. *Candida* osteomyelitis or joint infections can occur as complications after an episode of central venous catheter–related candidemia. Endophthalmitis may present as long as 1 month after initial fungemia, and the guidelines of the Infectious Diseases Society of America recommend eye examination for all patients with candidemia within the first week of presentation in nonneutropenic hosts and delayed examination until neutrophil recovery in neutropenic hosts. For central venous catheter–related candidemias, catheter removal followed by antifungal therapy with fluconazole, an echinocandin (such as caspofungin), or amphotericin B, based on susceptibility testing, should be administered.

Injection drug use is a risk factor for *Candida* endocarditis (and joint space infections, especially of the sternoclavicular joint). It is often caused by species other than *C albicans*. Echinocandin therapy is recommended as the initial therapy in the setting of candidemia, while identification and antimicrobial susceptibility results are pending, before de-escalation to azole therapy. Fluconazole is an appropriate alternative regimen in some patients, including those who are not critically ill and not thought to be at risk of azole-resistant *Candida* infection.

Candida urinary tract infection is common in patients with urinary catheters and those receiving antibacterial drugs. Removal of the catheter is the primary therapy. If necessary, treatment with fluconazole or bladder irrigation with dilute amphotericin B may be curative, although recurrence is common.

Hepatosplenic candidiasis, also called *chronic disseminated candidiasis*, typically occurs during the recovery phase after prolonged neutropenia. This condition is now rare because of frequent use of azole prophylaxis in neutropenic patients in current practice. When it does occur, fever, abdominal pain, and increased alkaline phosphatase level suggest the diagnosis. Typical "bull's-eye lesions" can be seen with ultrasonography, computed tomography, or magnetic resonance imaging of the infected liver. Fluconazole is the preferred antifungal agent in clinically stable patients; however, amphotericin B or an echinocandin is an option in ill patients or patients with refractory disease.

Candida esophagitis is a common cause of odynophagia in immunosuppressed patients, especially those with AIDS. Endoscopy is necessary to prove the diagnosis. *Candida* esophagitis is clinically indistinguishable from, and may coexist with, cytomegalovirus and herpes simplex virus esophagitis. Fluconazole is effective therapy for oral or esophageal candidiasis, although amphotericin B or an echinocandin may be needed for resistant organisms.

KEY FACTS

- ✓ Injection drug use is a risk factor for *Candida* endocarditis (and infections of joint space, especially the sternoclavicular joint). It is often caused by species other than *C albicans*
- ✓ *Candida* esophagitis is a common cause of odynophagia in immunosuppressed patients, especially those with AIDS. Endoscopy is necessary to prove the diagnosis

Mucormycosis (*Rhizopus* Species, Zygomycetes)

Mucormycosis is a term used to describe infections caused by fungi of the order Mucorales, such as *Mucor* and *Rhizopus*. Mucormycosis is a disease of immunocompromised hosts, primarily persons with impaired neutrophil number or function. Pulmonary, nasal, and sinus infections are the most common manifestations. Facial pain, headache, and fever are common symptoms. Rhinocerebral mucormycosis results from direct extension into the brain. Diabetic ketoacidosis, neutropenia, renal failure, and deferoxamine therapy are all risk factors for this life-threatening infection. The diagnosis of mucormycosis depends on finding the typical black necrotic lesions (usually in the nose or on the palate) and is confirmed by biopsy. Treatment involves reversing the predisposing condition as much as possible, prompt surgical débridement of necrotic tissue, and high-dose amphotericin B therapy. Posaconazole and isavuconazole are 2 azoles with activity against mucormycosis and can be used in step-down therapy.

Viruses

Herpesviruses

There are now 8 known human herpesviruses: herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpesvirus (HHV) 6 (HHV-6), HHV-7 (not yet known to be associated with a clinical disease), and HHV-8. All herpesviruses are DNA viruses that establish latency after primary infection, with or without symptoms.

Serologic evidence of infection is common by adulthood: HSV-1, 87%; HSV-2, 20%; VZV, 90%; EBV, 95%; and CMV, 50%. The rate of infection is greater in populations of lower socioeconomic status than of high socioeconomic status.

Herpes Simplex Virus

Primary infection with HSV results from exposure of skin or mucous membranes to intact viral particles. Latent infection is then established in sensory nerve ganglia. Genital HSV infection is caused by HSV type 2 in 80% of cases and by HSV type 1 in the remaining 20%, although these trends are changing. The converse is true for oral HSV infection. Genital HSV infection is more likely to recur when caused by HSV type 2. Recurrence rates of oral and genital HSV infection can be decreased by 80% with long-term use of antiviral drugs, an effect that then leads to decreased transmission to partners. Acyclovir, valacyclovir, and famciclovir are effective antiviral medications for treatment of primary or recurrent HSV infection.

Herpes simplex encephalitis is a nonseasonal, life-threatening illness usually caused by HSV type 1. It causes confusion, fever, and seizures. Simultaneous herpes labialis is present in 10% to 15% of cases. Magnetic resonance imaging of the brain, which shows characteristic temporal lobe involvement, and polymerase chain reaction assay for HSV from CSF are extremely sensitive. Detecting periodic lateralized epileptiform discharges with electroencephalography is suggestive of HSV encephalitis. Older age, poor neurologic status at presentation, and encephalitis of longer than 4 days before the initiation of therapy with IV acyclovir are associated with a poor outcome. The poor outcome with delayed antiviral therapy highlights the importance of prompt empiric initiation of antiviral therapy when HSV encephalitis is suspected.

Neonatal HSV infection is acquired at the time of vaginal delivery. The mortality rate is high (20%) despite antiviral therapy. In neonates who survive, neurologic sequelae and recurrent HSV lesions are common. Cesarean section is recommended when a woman has active herpetic lesions at the time of delivery.

HSV pneumonia is rare and usually occurs in immunosuppressed persons. When HSV is isolated from a respiratory source, it most commonly represents shedding from the oral mucosa rather than the lungs. HSV also is associated with visceral disease (such as esophagitis). Biopsy is required to reliably distinguish HSV from CMV or *Candida* esophagitis. **Herpetic whitlow** is a painful HSV infection of a finger that is most commonly acquired through contact with oral secretions. Health care professionals at risk are respiratory technicians, dentists, dental hygienists, and anesthesiologists.

KEY FACT

- ✓ Genital HSV infection is caused by HSV-2 in 80% of cases and by HSV-1 in the remaining 20%

Key Definition

Herpetic whitlow: *A painful HSV infection of a finger that is most commonly acquired through contact with oral secretions.*

Varicella-Zoster Virus

Before the availability of routine vaccination against VZV, primary infection with the virus commonly occurred in childhood and caused chickenpox, an illness characterized by fever and a generalized vesicular eruption (dewdrop on a rose petal). Illness with chickenpox is more likely to be severe in adults and immunocompromised persons. Varicella pneumonia occurs in 5% to 50% of chickenpox cases. Pregnant women are especially vulnerable and should be treated with high-dose IV acyclovir. Pneumonia develops within 1 to 6 days after the onset of illness with primary VZV infection. Encephalomyelitis is another serious complication, occurring predominantly in children. Typical onset is 3 to 14 days after the appearance of rash.

After primary infection, VZV DNA persists in a latent state in sensory nerve ganglia. Reactivated infection causes zoster (shingles), which manifests as a painful vesicular rash in a dermatomal distribution. Involvement of the fifth cranial nerve, especially the ophthalmic branch, may threaten the person's vision. Neurologic complications of VZV include motor paralysis (localized to the dermatomal distribution of rash), encephalitis, and myelitis.

Varicella immune globulin can prevent primary VZV infection and is recommended within 10 days of exposure in the following: 1) pregnant women who lack immunity to VZV, 2) immunocompromised patients without immunity to VZV, 3) neonates whose mothers have signs and symptoms of varicella around the time of delivery (ie, 5 days before through 2 days after delivery), and 4) premature infants with exposure history.

Chickenpox (primary VZV infection) is treated with acyclovir, valacyclovir, or famciclovir to reduce the severity and duration of illness, as well as to reduce complications from infection. Zoster should also be treated with acyclovir, valacyclovir, or famciclovir to reduce illness duration and to prevent postherpetic neuralgia. Corticosteroid use for the prevention of postherpetic neuralgia remains controversial. For disseminated zoster infections (eg, encephalitis, cranial neuritis), high-dose IV acyclovir decreases the duration of hospitalization pending clinical improvement, and this management is followed by transition to oral antiviral therapy.

Two effective VZV vaccines are available. A live-attenuated VZV vaccine is part of the routine childhood vaccine series for primary prevention of varicella infection. A new recombinant adjuvanted VZV vaccine was recently approved for herpes zoster prevention in patients 50 years or older and is now the preferred vaccine for herpes zoster prevention, replacing the high-dose live-attenuated VZV vaccine.

Epstein-Barr Virus

Most acute EBV infections are asymptomatic. Symptomatic infectious mononucleosis due to EBV infection causes the clinical triad of fever, pharyngitis (in 80% of cases), and adenopathy. Splenomegaly occurs in 50% of cases. A rare, but serious, complication of mononucleosis is splenic rupture (may occur spontaneously, typically at 1-2 weeks after initial symptoms). Other complications include hemolytic anemia, airway obstruction, encephalitis, transverse myelitis, and, rarely, hemophagocytic lymphohistiocytosis. Associated laboratory abnormalities include atypical lymphocytosis, thrombocytopenia, and mild increases in liver enzyme values.

Corticosteroids are indicated for hemolytic anemia, severe thrombocytopenia, and acute airway obstruction. Ampicillin or amoxicillin given during infectious mononucleosis commonly causes a diffuse macular rash.

Table 46.1 differentiates EBV from other causes of mononucleosis. The diagnosis of infectious mononucleosis depends on detection of heterophile antibodies (monospot test) or specific

Table 46.1 • Infectious Mononucleosislike Diseases

	Findings					
Disease	**Pharyngitis**	**Adenopathy**	**Splenomegaly**	**Atypical Lymphocytes**	**Heterophile Antibodies**	**Other Test Findings**
Infectious mononucleosis	++++	++++	+++	+++	+	Specific EBV antibody + VCA IgM
CMV	–	–	+++	++	–	CMV IgM
Toxoplasmosis	–	++++	+++	++		Toxoplasmosis serology
HIV infection	+	+++	–	++	–	HIV serology (will likely be negative in acute infection) HIV viral load

Abbreviations and symbols: CMV, cytomegalovirus; EBV, Epstein-Barr virus; IgM, immunoglobulin M; VCA, viral capsid antigen; –, absent; +, ++, +++, and ++++, present to various degrees.

EBV IgM antibodies. False-negative results of the monospot test are more likely with increasing patient age.

Uncomplicated cases of EBV require symptomatic care only. The patient should not participate in contact sports for several months because of the risk of splenic rupture. Corticosteroids are not indicated for uncomplicated infection. Acyclovir and other antiviral drug therapy are not effective against EBV.

KEY FACT

✓ Symptomatic infectious mononucleosis causes the clinical triad of fever, pharyngitis (in 80% of cases), and adenopathy

Cytomegalovirus

Primary CMV infection is usually asymptomatic, but it can cause a heterophile-negative mononucleosis syndrome. It is a substantial cause of neonatal disease. Perinatal infection can occur in utero, intrapartum, or postpartum and can cause congenital malformations. Primary infection of a woman during pregnancy results in a 15% chance of fetal cytomegalic inclusion disease. Young children in day care centers commonly shed CMV in their urine and saliva. Parents are at risk of acquiring primary infection from asymptomatic children. CMV can cause fever of unknown origin in healthy adults, especially in those with children of day care age.

In persons with impaired cellular immunity (such as persons with AIDS or organ and bone marrow transplant recipients), CMV causes serious infections: retinitis, pneumonia, gastrointestinal tract ulcerations, encephalitis, and adrenalitis. The diagnosis is most often established through isolation of CMV from blood or from culture, polymerase chain reaction assay of blood, histopathologic evidence of CMV infection in involved tissue (eg, liver, lung, gastrointestinal tract), or clinical findings alone (such as CMV retinitis).

CMV disease in persons with AIDS is almost always caused by reactivation of latent infection. Finding CMV in the blood or urine of patients with AIDS is common and has a low predictive value for symptomatic CMV disease. CMV retinitis occurs in 20% to 30% of patients with advanced AIDS. Its diagnosis is based on ophthalmologic examination (from a finding of “ketchup and mustard retina”). The relapse rate for CMV retinitis in AIDS is high, even with long-term antiviral therapy.

Solid organ and bone marrow transplant recipients are another group of patients at risk for CMV disease.

Symptomatic disease (called *CMV syndrome*) usually develops in the first 4 to 8 weeks after a solid organ transplant and causes fever, leukopenia, increases in liver enzyme values, and end-organ involvement. CMV serum antigen testing or the more commonly used CMV polymerase chain reaction assay helps confirm the diagnosis. Patients who have had bone marrow transplant are especially at risk for CMV pneumonia. The mortality rate approaches 50% despite therapy.

Immunocompetent patients with CMV typically do not require treatment. Ganciclovir is the treatment of choice for most CMV infections in immunocompromised hosts. Full-dose induction therapy is given for 2 to 3 weeks, followed by maintenance therapy for 2 to 3 months. Oral valganciclovir has excellent bioavailability and can be used for maintenance therapy or suppression.

KEY FACT

✓ Primary CMV infection is usually asymptomatic, but it can cause a heterophile-negative mononucleosis syndrome

Human Herpesvirus 6

HHV-6 is a recently discovered lymphotropic virus. It causes the mild childhood infectious exanthem known as *roseola infantum*. Similar to CMV, the reactivation of HHV-6 infection occurs after organ transplant. HHV-6 has been associated with encephalitis and pneumonitis after bone marrow transplant.

Human Herpesvirus 8

HHV-8 is associated with Kaposi sarcoma in patients with HIV infection. HHV-8 has also been linked to other body cavity–based lymphomas in patients with AIDS and Castleman disease.

Measles (Rubeola)

Measles cases started to increase substantially in the late 1990s in unvaccinated children. Outbreaks of measles are still occurring in the United States, primarily in previously nonimmunized persons. Prodromal upper respiratory tract symptoms are prominent. Blue-gray oral lesions (Koplik spots) precede the measles rash.

Complications of measles include encephalitis and pneumonia. Encephalitis is often severe and usually occurs after a period of apparent improvement of measles infection. Secondary bacterial infection is more common than primary measles pneumonia. *Staphylococcus aureus* and *Haemophilus influenzae* are the most common bacterial pathogens.

Rubella

The prodromal symptoms of rubella are mild (unlike those of measles). Posterior cervical lymphadenopathy, arthralgia (70% in adult cases), transient erythematous rash, and fever are characteristic. Infection is subclinical in many cases. CNS complications and thrombocytopenia are rare. The greatest danger from rubella is fetal infection in unimmunized pregnant women, which can result in congenital rubella syndrome or fetal demise. The risk varies from 40% to 60% when infection occurs during the first 2 months of gestation to 10% by the fourth month. Intravenous gamma globulin may mask symptoms of rubella in pregnant women, but it does not protect the fetus.

From 6% to 11% of young adults continue to be susceptible to rubella after receiving the rubella vaccine. A pregnant woman should not be given rubella vaccine because it can cause congenital abnormalities. Women of childbearing age should be warned not to become pregnant within 2 to 3 months from the time of immunization. Transient arthralgias develop in 25% of immunized women. Fever, rash, and lymphadenopathy also may develop. Symptoms may occur as long as 2 months after vaccination.

Mumps

Mumps virus can be transmitted by direct contact with respiratory droplets, saliva, or contaminated fomites. The incubation period is 16 to 18 days (range, 12-25 days) from exposure to onset of symptoms. Mumps virus commonly affects glandular tissue. Parotitis, pancreatitis, and orchitis are characteristic manifestations. Orchitis occurs in 20% of boys and men with mumps. It is unilateral in approximately 75%. Orchitis often is associated with recrudescence of fever, malaise, chills, and testicular pain. Sterility is uncommon, even after bilateral infection. Before mumps vaccination became routine, mumps meningoencephalitis was one of the most common nonseasonal viral meningitides. It can cause low glucose levels in CSF, mimicking bacterial meningitis. Although mumps cases are uncommon in the United States, outbreaks have been identified, largely in unvaccinated children.

Clinical suspicion of mumps can be confirmed by serologic test (IgM for mumps) within 5 days of illness onset or sending a parotid duct swab or other samples such as CSF for viral cultures.

KEY FACT

✓ Parotitis, pancreatitis, and orchitis are characteristic manifestations of mumps

Parvovirus B19

Parvovirus B19 is a single-stranded DNA virus that infects the erythrocyte precursors in bone marrow, with resulting reticulocytopenia. It is the cause of erythema infectiosum (fifth disease) in children, transient arthritis in adults (which is symmetrical, involves small joints, and can mimic rheumatoid arthritis), and aplastic crisis in persons with hemolytic anemias. Infection during pregnancy results in a 5% chance of hydrops fetalis or fetal death. Serologic testing is the preferred diagnostic method in immunologically competent persons.

Parvovirus B19 infection may persist in immunosuppressed patients, resulting in red blood cell aplasia. Diagnosis is established by the finding of giant pronormoblasts in bone marrow or the identification of viral DNA in bone marrow or peripheral blood. Most patients respond to administration of immune globulin infusions for 5 to 10 days. No treatment is recommended for parvovirus infections in immunocompetent patients.

KEY FACT

✓ Parvovirus is the cause of transient arthritis in adults (which is symmetrical, involves small joints, and can mimic rheumatoid arthritis) and aplastic crisis in persons with hemolytic anemias

Human T-Cell Lymphotropic Viruses

Human T-cell lymphotropic virus (HTLV) types I and II are non-HIV human retroviruses. HTLV-I is endemic in parts of Japan, the Caribbean basin, South America, and Africa. It can be transmitted through sexual contact, infected cellular blood products (not clotting factor concentrates), and injection drug use. Vertical transmission (eg, breast-feeding, transplacental) also occurs. HTLV-I is associated with human T-cell leukemia or lymphoma and tropical spastic paraparesis (also known as *HTLV-I–associated myelopathy*). However, clinical disease never develops in 96% of persons infected with HTLV-I. An HTLV-II infection is not known to cause clinical disease.

Parasites

Helminths

Neurocysticercosis is an infection of the CNS with the larval stage of the pork tapeworm, *Taenia solium*. It is acquired by ingesting tapeworm eggs from fecally contaminated food (not from eating undercooked pork). It is endemic in Latin America, Asia, and Africa. Cases have been reported among household contacts of foreign-born persons (working as domestic employees). The most common presentation is seizures. Brain imaging reveals cystic or calcified brain lesions. Serum or CSF serologic testing can aid in the diagnosis. Treatment with praziquantel or albendazole may be beneficial. Coadministration of corticosteroids often is used to decrease cerebral inflammation associated with therapy.

Strongyloides stercoralis is unique among the intestinal nematode infections. Unlike with the other helminths, the larvae of this organism can mature in the human host (autoinfection). In the United States, the majority of cases occur in the southeastern states or in travelers from endemic areas. In immunocompromised hosts (eg, persons with neutropenia, those receiving corticosteroid therapy, or those with AIDS), a superinfection can develop with larval migration throughout the body, and infection can persist for years or even decades. Gram-negative bacteremia is a common coinfection, resulting from disruption of the intestinal mucosa by the invasive larvae. Treatment is with ivermectin.

Trichinosis is acquired from eating undercooked meat, particularly bear or cougar. Features include muscle pain (especially diaphragm, chest, and tongue), eosinophilia, and periorbital edema. Treatment is with mebendazole or albendazole.

Hookworm (*Necator americanus*) infection causes anemia. It is found mainly in tropical and subtropical regions. The larval form can penetrate intact skin. Walking barefoot is a risk factor for infection. Treatment is with mebendazole or albendazole.

Ascariasis infection may cause intestinal obstruction or pancreatitis (ie, the worm migrates up the pancreatic duct). Treatment is with mebendazole or albendazole.

Schistosomiasis is a tropical disease that causes hepatic cirrhosis, hematuria, and carcinoma of the bladder. It is acquired by direct penetration of *Schistosoma cercariae* organisms from contaminated water (eg, lakes, rivers). Praziquantel is the drug of choice for schistosomiasis.

Protozoan Parasites

Acanthamoeba, a free-living ameba, can cause amebic keratitis in persons swimming in freshwater while wearing soft contact lenses. The diagnosis is based on microscopic examination of scrapings of the cornea. Treatment is with topical antifungal agents. Patients often respond poorly to therapy and have progressive corneal destruction.

Symptomatic infection with *Entamoeba histolytica* (amebiasis) may cause diarrhea (often, bloody diarrhea), abdominal pain, and fever. Metronidazole administration, followed by a luminal agent such as iodoquinol or paromomycin, is the preferred therapy (metronidazole does not kill amebae in the intestinal lumen). Asymptomatic carriage of amebic cysts should be treated with one of the luminal agents.

Invasive amebiasis may lead to distant abscesses (primarily of the liver, but other organs can be involved). An amebic liver abscess usually is a sole abscess commonly located in the right lobe of the liver. The anatomical location and the fact that it is usually a single abscess may help to distinguish amebic hepatic abscess from bacterial abscess. Serologic tests are positive in more than 90% of patients with amebic abscess. Hepatic abscess may rupture into the peritoneal cavity or through the diaphragm into the right pleural space.

Giardia lamblia infection characteristically produces sudden onset of watery diarrhea with malabsorption, bloating, and flatulence. Prolonged disease that is refractory to standard therapy may occur in patients with IgA deficiency. The organism may be detected with antigen testing of stool specimens, a test that has high sensitivity. Metronidazole, tinidazole, or nitazoxanide is effective for treating giardiasis.

Toxoplasma gondii is acquired from eating undercooked meat or being exposed to cat feces. Primary toxoplasmosis is usually asymptomatic. In immunocompetent persons, it may cause a heterophile-negative mononucleosislike syndrome. *Toxoplasma* chorioretinitis can occur in immunocompetent persons during primary infection. A person with toxoplasmosis may present with fever and blurry vision. On ophthalmologic examination, an acute retinochoroiditis causes marked vitreous reaction overlying the retinal infection, leading to the characteristic fundus picture of the optic nerve appearing as a "headlight in the fog." Reactivation disease can cause brain and eye lesions and pneumonia in patients with AIDS and other immunocompromising conditions. Toxoplasmosis can be treated effectively with pyrimethamine in combination with either sulfadiazine or clindamycin; trimethoprim-sulfamethoxazole is likely an effective alternative regimen, particularly in resource-limited settings.

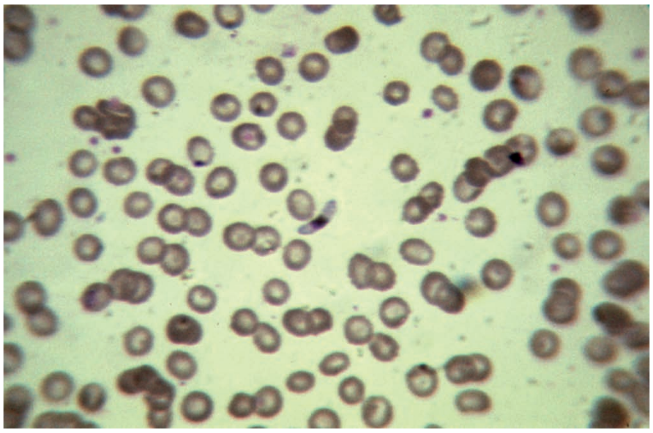

Figure 46.6. *Banana-Shaped Gametocyte of* Plasmodium falciparum *in Thin Blood Smear.*

Malaria is caused by *Plasmodium* parasites and is endemic in many parts of the world. It is transmitted by *Anopheles* species mosquitoes that typically bite at night and predawn. After it enters human blood from mosquito bite, the parasite first matures in the liver and then infects erythrocytes. Spiking fevers, rigors, headache, and hemolytic anemia are the hallmarks of malaria. It is diagnosed through examination of Giemsa-stained thick and thin blood smears (Figure 46.6). Polymerase chain reaction tests are available to confirm the diagnosis microscopically or in the clinical setting of low-level parasitemia. *Plasmodium falciparum* is the most common cause of fever in a traveler returned from Africa and is more likely to cause malarial complications, such as cerebral malaria, pulmonary edema, and death. With *P falciparum* malaria, fevers may be irregular or continuous. *Plasmodium vivax* and *Plasmodium malariae* infections cause regular episodic fevers (malarial paroxysms). *Plasmodium vivax* and *Plasmodium ovale* have hypnozoite forms that can remain latent in the liver and cause relapsing infection.

Chloroquine is the preferred treatment of infection caused by *P ovale, P vivax, P malariae*, and known chloroquine-susceptible strains of *P falciparum*. Chloroquine-resistant strains of *P falciparum* may respond to quinine and doxycycline, atovaquone-proguanil hydrochloride, mefloquine, or artemisinin derivatives (available in the United States only through the Centers for Disease Control and Prevention). For severe *P falciparum* infection, IV quinidine gluconate is effective; however, resistant cases of *P falciparum* might require treatment with doxycycline or clindamycin. Exchange transfusion may be beneficial for severely ill patients with parasitemia of more than 10%. Primaquine is needed to eradicate the exoerythrocytic phase of *P ovale* and *P vivax* infections and thereby prevent relapses.

Prophylaxis for malaria is increasingly difficult because of drug-resistant *P falciparum*. Personal protection should always be used (eg, mosquito nets, insect repellents containing diethyltoluamide). For travelers to chloroquine-sensitive areas—Central America, Mexico, Haiti, the Dominican Republic, and the Middle East—chloroquine is still effective therapy. In chloroquine-resistant areas, mefloquine, doxycycline, or an atovaquone-proguanil combination tablet is suggested. Travelers to the mefloquine-resistant areas of the Thai-Myanmar and Thai-Cambodian borders should use doxycycline or atovaquone-proguanil. Protection resulting from these medications ranges from 90% to 95%. All patients should be advised to seek medical attention if fever develops within 1 year after return from an endemic area.

Leishmaniasis is a protozoan disease transmitted by the bite of a sand fly. Visceral leishmaniasis (kalaazar, caused by *Leishmania donovani*) causes fever, hepatosplenomegaly, cachexia, and pancytopenia. Bone marrow examination (Giemsa stain) is often diagnostic. Cutaneous leishmaniasis (caused by *Leishmania tropica, Leishmania major, Leishmania braziliensis*, and *Leishmania mexicana*) occurs as a painless papule that progresses to an ulcer and may be self-limited. Cutaneous leishmaniasis has occurred in military personnel returning from Iraq (the so-called Baghdad boil) and Afghanistan. Cutaneous leishmaniasis lesions are often destructive and should be treated. Leishmaniasis treatment is antimony compounds or amphotericin B or its liposomal formulations.

Babesia microti is a tick-borne illness transmitted by the same *Ixodes* tick that is responsible for Lyme disease and ehrlichiosis. This parasite infects erythrocytes and causes fever, myalgias, and hemolytic anemia. Often asymptomatic in healthy persons, severe disease may develop in asplenic individuals. Babesiosis is endemic in the northeastern United States, especially around Nantucket, Martha's Vineyard, and Cape Cod, Massachusetts. The diagnosis is established through examination of a peripheral blood smear or polymerase chain reaction amplification of *Babesia* DNA from peripheral blood. Treatment is with clindamycin and quinine for severe disease or atovaquone plus azithromycin for mild-to-moderate disease. Exchange transfusion has been needed in severely ill patients with high-level parasitemia. Simultaneous infection with babesiosis and Lyme disease may be especially severe.

KEY FACTS

- ✓ Chloroquine is the preferred treatment of infection by *P ovale, P vivax, P malariae*, and the known chloroquine-susceptible strains of *P falciparum*
- ✓ Chloroquine-resistant strains of *P falciparum* may respond to quinine and doxycycline, atovaquone-proguanil, mefloquine, or artemisinin derivatives (available in the United States only through the Centers for Disease Control and Prevention)
- ✓ Leishmaniasis is a protozoan disease transmitted through the bite of a sand fly

Key Definition

Neurocysticercosis: *An infection of the CNS with the larval stage of the port tapeworm,* Taenia solium.

47 Health Care–Associated Infections and Infective Endocarditis

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Health Care–Associated Infections

Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) account for 25% of all infections in the intensive care unit and are the basis for 50% of all antimicrobials prescribed in the hospital. HAP is pneumonia that develops in a nonintubated patient more than 48 hours after hospital admission. VAP develops in a patient more than 48 hours after intubation. These are primarily bacterial infections and are associated with high morbidity and mortality rates. However, pneumonias occurring before the fifth day of hospitalization are generally caused by organisms that are more susceptible to antimicrobials and have a better prognosis than those occurring on or after the fifth hospital day. The diagnostic and therapeutic approaches to HAP and VAP are similar and should take into account the local antibiogram (antibiotic susceptibility and resistance patterns among isolates at the hospital or particular unit) for empirical therapy.

Updated guidelines by the Infectious Diseases Society of America in 2016 recommended removing the classification of health care–associated pneumonia. Patients with health care–associated pneumonia were thought to be at high risk for multidrug-resistant (MDR) organisms given their contact with the health care system. However, evidence did not support this notion because most of the affected patients were not at high risk for MDR organisms.

Key Definition

Hospital acquired pneumonia: *This is pneumonia that develops in a nonintubated patient more than 48 hours after hospital admission.*

The common microbiologic causes of HAP and VAP are summarized in Box 47.1. The general principles for treatment and prevention of HAP and VAP are listed in Box 47.2.

HAP or VAP should be suspected when a patient has clinical signs of lower respiratory tract infection, such as fever, purulent sputum, leukocytosis, decline in oxygenation, and a new infiltrate on chest imaging. Blood and lower respiratory tract secretions (eg, from endotracheal aspiration) should be cultured before starting or changing antimicrobial therapy. However, initiation of antimicrobial therapy should not be delayed while awaiting culture results. If a patient has marked clinical improvement within 48 to 72 hours of starting empirical antimicrobial therapy and sputum test results are negative, use of antimicrobials can safely be discontinued.

Empirical antimicrobial therapy should be based on local antibiograms, ideally one that is specific to the intensive care unit population. Patient risk factors must also be considered when deciding empirical antibiotic coverage for MDR organisms, particularly *Staphylococcus aureus, Pseudomonas aeruginosa*, and other gram-negative bacilli. A major risk factor for both MDR HAP and VAP is the use of intravenous antibiotics within

Box 47.1 • Common Microbiologic Causes of HAP and VAP

Pseudomonas aeruginosa
Klebsiella species
Serratia species
Escherichia coli
Staphylococcus aureus, including methicillin-resistant *S aureus*
Proteus mirabilis
Citrobacter species
Enterobacter species
Acinetobacter species
Stenotrophomonas maltophilia

Abbreviations: HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia.

Box 47.2 • General Principles for Treatment and Prevention of HAP and VAP

1. Early recognition and start of empirical therapy (because morbidity and mortality rates increase with delays in initiation of antimicrobial treatment)
2. Choice of empirical therapy based on local antibiograms for susceptibility and resistance data
3. Antimicrobials stewardship to reduce unnecessary antimicrobial use and selection pressure for resistant organisms
4. Implement prevention strategies
    - General
        - Staff education and hand hygiene
        - Surveillance of infections in the intensive care unit, including susceptibility testing
    - Aspiration precautions
        - Semirecumbent position (30°-45°), rather than supine
        - Preference of enteral feeding over parenteral nutrition
    - Intubation and mechanical ventilation
    - Strategies to avoid re-intubation
        - Noninvasive ventilation should be used when possible in selected patients
        - Orotracheal and orogastric tubes are preferred over nasotracheal and nasogastric tubes
        - Continuous aspiration of subglottic secretions should be performed
        - Endotracheal tube cuff pressure maintenance at >20 cm H_2O
        - Contaminated condensate should be carefully removed from ventilator circuits
        - Protocols to reduce sedation and accelerate weaning should be enacted

Abbreviations: HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia.

the past 90 days. Risk factors for MDR VAP also include septic shock at the time of VAP, acute respiratory distress syndrome preceding VAP, 5 or more days of hospitalization before the occurrence of VAP, and acute renal replacement therapy before VAP onset. Furthermore, if a patient is hospitalized in a unit where 10% to 20% or more of *S aureus* isolates are methicillin-resistant (MRSA) or the prevalence of MRSA is not known or if a patient has a high risk for mortality, then the use of vancomycin or linezolid for coverage is appropriate.

The use of 2 antipseudomonal antibiotics from different classes for suspected VAP is recommended for patients with MDR risk factors, patients in units where more than 10% of gram-negative isolates are resistant to an agent being considered for monotherapy, and patients in an intensive care unit where local susceptibilities are not available. In patients without these risks factors, the use of only 1 antipseudomonal antibiotic is recommended.

The recommended duration of antibiotic therapy in patients with VAP or HAP is 7 days. Shorter or longer durations of treatment may be indicated on the basis of a patient's clinical status.

KEY FACTS

✓ HAP and VAP account for 25% of intensive care unit infections. They are the reason for 50% of all antimicrobials prescribed in US hospitals

✓ HAP, VAP, and health care–associated pneumonia are primarily bacterial infections that are associated with high morbidity and mortality rates

Catheter-Related Bloodstream Infection

In the United States, approximately 5 million central venous catheters are placed annually. About 1 in 20 of these catheters becomes infected. Indeed, catheter-related bloodstream infection (CR-BSI) is the most common cause of health care–associated bacteremia in the United States. CR-BSI is associated with substantial cost (about $28,000 per survivor), increased length of stay (average, 6.5 days), and a substantial mortality rate (10%-25%).

Catheter infection may present with local manifestations (port, tunnel, or exit site infection) or CR-BSI. Local infections are easy to recognize and always necessitate removal of the infected catheter. However, CR-BSI may present with no inflammatory signs or drainage from the exit site or tunnel. In these situations, blood should be simultaneously drawn from the catheter and a peripheral site. If cultures of blood drawn from the catheter have positive results 2 hours before the cultures from the peripheral site (differential time to positivity), this finding has high correlation (>80%) with catheter infection. If the catheter is urgently removed (eg, because of absence of an alternative source of infection, because of hemodynamic instability of the patient), the catheter tip should be submitted for culture. Growth of more than 15 colony-forming units (per milliliter) of bacteria is highly suggestive of the catheter being the source of bloodstream infection.

Removal of the infected catheter is always the preferred method for treating CR-BSI. Short-term catheters (temporary central venous catheters or peripherally inserted central catheter) should always be removed to treat CR-BSI. However, long-term tunneled catheters (for hemodialysis, chemotherapy, or parenteral nutrition) may be salvaged in patients who are clinically stable, have infection with a low-virulence organism (such as *Staphylococcus epidermidis*), and have bloodstream infection that quickly resolves with therapy. Antibiotic lock therapy, in combination with systemic antimicrobial agents, is a key ingredient of catheter salvage attempts. A clinically unstable patient, the presence of local or systemic complications, and infection with virulent organisms (such as *S aureus, Candida*, or gram-negative bacteria) warrant removal of an infected, long-term, tunneled catheter.

KEY FACTS

- ✓ CR-BSI is the most common cause of health care–associated bacteremia in the United States
- ✓ Catheter infection may present with local manifestations (infection at the port, tunnel, or exit site) or catheter-related bloodstream infection. Local infections are easy to recognize and necessitate catheter removal
- ✓ Catheter-related bloodstream infection may present with no inflammatory sign or drainage from the exit site or catheter tunnel. In such situations, blood should be drawn simultaneously from the catheter and a peripheral site
- ✓ When cultures of blood drawn from the catheter test positive 2 hours before the cultures from the peripheral site (ie, differential time to positivity), this finding correlates more than 80% with catheter infection
- ✓ The catheter tip should be submitted for culture. Growth of more than 15 colony-forming units (per milliliter) of bacteria is highly suggestive that the catheter is the source of bloodstream infection

Common Nosocomial Pathogens

Staphylococcus aureus

Staphylococcus aureus is a common cause of **nosocomial infections**, including surgical site infections, CR-BSI, and VAP. When nosocomial *S aureus* bacteremia is caused by a removable focus of infection (such as a venous catheter), a 2-week course of therapy may be sufficient if the infected catheter is quickly removed and clearance of bacteremia is rapid. However, most cases of community-acquired *S aureus* bacteremia should be treated parenterally for 4 weeks. Therapy may be extended to 6 weeks or longer in patients with infective endocarditis, bone and joint infection, and septic thrombosis. Patients who present with community-onset *S aureus* bacteremia, have blood cultures positive for more than 3 days, or have an implanted cardiac device (pacemaker or defibrillator) should undergo transesophageal echocardiography to screen for endocarditis. Urine cultures that are positive for *S aureus* should raise concern for *S aureus* bacteremia with secondary seeding of the urinary tract.

Key Definition

Nosocomial infections: *These are acquired in hospitals and other health care facilities. (The term* nosocomial *comes from 2 Greek words:* nosus, *meaning* disease, *and* komeion, *meaning* to take care of.*) Patients must have had no signs of active infection on admission. These infections occur up to 48 hours after hospital admission and up to 3 days after discharge.*

Most *S aureus* strains produce β-lactamase (a penicillinase) and thus are resistant to penicillin G or amoxicillin but are susceptible to β-lactam–β-lactamase inhibitor combination drugs, such as amoxicillin-clavulanic acid. The semisynthetic penicillins (eg, nafcillin, oxacillin) and first-generation cephalosporins stay active and are drugs of choice against methicillin-sensitive *S aureus* strains. *S aureus* resistance to the β-lactam antibiotics is caused by an alteration of the penicillin-binding proteins in the cell wall. The MRSAs are resistant to all β-lactam antibiotics but continue to have susceptibility to such drugs as vancomycin, linezolid, ceftaroline, and daptomycin.

Treatment of *S aureus* isolates, based on the susceptibility testing, is summarized in Table 47.1. Vancomycin is the most reliable and well-studied drug for treating serious MRSA infections, and its efficacy is equivalent to that of daptomycin. Of note, daptomycin is not active in lungs and should not be used to treat MRSA pneumonia. Oral antibiotics active against MRSA (trimethoprim-sulfamethoxazole or tetracyclines) are primarily used to treat skin and soft tissue infections or to provide chronic suppression of hardware-associated *S aureus* infections after completion of a parenteral antibiotic course for acute infection.

Staphylococcus aureus frequently colonizes the nares and thereby increases the risk of infection. Topical mupirocin ointment or oral trimethoprim-sulfamethoxazole (with or without rifampin) may temporarily eradicate the nasal colonization and is helpful for reducing the rate of postoperative wound infection. However, recolonization after a short interval is frequent.

Coagulase-Negative Staphylococci

Staphylococcus epidermidis is the most common of the coagulase-negative staphylococci (CoNS) and is part of normal skin flora. *Staphylococcus lugdunensis* is a CoNS that tends to be more aggressive and clinically behaves like *S aureus*. CoNS are commonly associated with infection of medical devices (such as central venous catheters, pacemakers or defibrillators, prosthetic heart valves, and prosthetic joints) but rarely cause disease in otherwise healthy persons.

Determining the significance of blood cultures growing CoNS can be difficult. True infections generally result in systemic symptoms and multiple positive blood cultures, whereas a single positive blood culture is generally indicative of a contaminant.

Treatment of CoNS-associated medical device infections usually requires complete removal of the device and administration of appropriate antibiotics (Table 47.1). Although a catheter-related CoNS bacteremia can be adequately treated with antibiotics administered for 1 to 2 weeks, infection of a prosthetic heart valve or prosthetic joint caused by CoNS warrants a 6-week regimen of vancomycin, usually in combination with rifampin (because of its antibiofilm properties).

Pseudomonas aeruginosa

Pseudomonas aeruginosa is typically associated with nosocomial infection. Infections caused by *P aeruginosa* include folliculitis associated with hot tub use, osteomyelitis (particularly in injection drug users), malignant otitis externa in patients with diabetes mellitus, complicated urinary tract infections, VAPs, and pulmonary infections in patients with cystic fibrosis. Patients with neutropenia are also at high risk for *Pseudomonas* infection and bacteremia. Thus, the febrile patient with neutropenia should have empirical treatment with antipseudomonal antibiotics while culture results are pending. Ecthyma gangrenosum, a necrotizing skin lesion, may develop in neutropenic patients with bacteremia due to *P aeruginosa*. Agents active against most *P aeruginosa* organisms are listed in Table 47.1.

Infective Endocarditis

Infective endocarditis is universally fatal without treatment. The hallmark of endocarditis is formation of vegetations (a mass of fibrin, platelets, microcolonies of organisms, and scant inflammatory cells) on cardiac valves. Endocarditis can be broadly categorized into native and prosthetic valve endocarditis.

Native Valve Endocarditis

Native valve infective endocarditis is more common in men and patients older than 65 years. Mitral valve prolapse, bicuspid aortic valves, and aortic sclerosis are the principal predisposing valvular lesions in the absence of prosthetic materials.

Infective endocarditis may present acutely or subacutely, depending on the virulence of the infecting organism. In 75% of

Table 47.1 • Treatment of Specific Nosocomial Pathogens

Organism	First-Line Treatment	Alternative Treatment
Penicillin-sensitive *Staphylococcus* (rare)	Penicillin	Any of the agents listed under first-line or alternative treatment below is active
Oxacillin- or methicillin-sensitive *Staphylococcus*	Nafcillin, oxacillin, first-generation cephalosporin, dicloxacillin	Clindamycin (if double-disk diffusion test is negative), TMP-SMX, minocycline; broad-spectrum agents with activity against oxacillin-sensitive staphylococci include cefepime, ceftriaxone, β-lactam/β-lactamase inhibitors, carbapenems, newer fluoroquinolone
Oxacillin-resistant *Staphylococcus* (MRSA, MRSE)	Vancomycin, linezolid, daptomycin, ceftaroline	Tigecycline; or, depending on susceptibility for mild to moderate infections or step-down therapy: TMP-SMX, minocycline, newer fluoroquinolone, dalfopristin-quinupristin
Vancomycin-intermediate or vancomycin-resistant *Staphylococcus* (VISA, VRSA)	Daptomycin	Ceftaroline, linezolid, tigecycline
Pseudomonas aeruginosa	Cefepime, ceftazidime, meropenem, or imipenem (not ertapenem); consider addition of aminoglycoside or ciprofloxacin for severe infection or until susceptibilities are known	Ciprofloxacin, levofloxacin, piperacillin-tazobactam, ceftazidime-avibactam, ceftolozane-tazobactam, colistin, aztreonam
Stenotrophomonas maltophilia	TMP-SMX (consider adding ticarcillin-clavulanate for severe infection)	Ticarcillin-clavulanate, tigecycline, fluoroquinolone, minocycline

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; TMP-SMX, trimethoprim-sulfamethoxazole; VISA, vancomycin-intermediate *Staphylococcus aureus*; VRSA, vancomycin-resistant *Staphylococcus aureus*.

patients with native valve endocarditis, clinical features include fever, malaise, weight loss, and skin lesions. Heart murmurs are described in 85% of patients, and up to one-third may have a new murmur. Atypical presentation is more frequent in the elderly population, especially with low-virulence organisms such as enterococci.

The diagnosis of infective endocarditis is based on the modified Duke criteria, which include pathologic, clinical, microbiologic, and echocardiographic findings (Boxes 47.3 and 47.4).

The microbiologic cause of endocarditis partly depends on whether the infection was acquired in the community or a health care setting. Most cases of community-acquired native valve endocarditis are due to viridans group streptococci (ie, *Streptococcus sanguis, Streptococcus mutans*, and *Streptococcus mitis*), *S aureus*, and enterococci. Less common causes include *Streptococcus bovis* (associated with gastrointestinal malignancy), *S pneumoniae*, CoNS (*S lugdunensis* has a response similar to that of *S aureus*), gram-negative bacilli, and fungi. In injection drug users, *S aureus* (60%), streptococci (16%), gram-negative bacilli (13.5%), polymicrobial infection (8.1%), and *Candida* species may be culprits. Tricuspid valve involvement is common in injection drug users and in patients with health care–associated endocarditis due to central venous catheters or implanted cardiac devices.

Box 47.3 • Modified Duke Criteria for the Diagnosis of Infective Endocarditis

Definite infective endocarditis

Pathologic criteria

Microorganisms on culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen,

or

Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis

Clinical criteria[a]

2 major criteria, *or*

1 major criterion and 3 minor criteria, *or*

5 minor criteria

Possible infective endocarditis

1 major criterion and 1 minor criterion, *or*

3 minor criteria

Rejected

Firm alternative diagnosis explaining evidence of infective endocarditis,

or

Resolution of infective endocarditis syndrome with antibiotic therapy for ≤4 d, *or*

No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for ≤4 d, *or*

Does not meet criteria for possible infective endocarditis, as above

[a] See Box 47.4 for definitions of major and minor criteria.

From Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000 Apr;30(4):633-8; used with permission.

Starting empirical antibiotic therapy before performing blood cultures is the most common cause of culture-negative endocarditis. Other reasons for culture-negative endocarditis include infection with fastidious organisms that are difficult to cultivate in blood cultures (Box 47.5). Several of these can be diagnosed with serologic tests or molecular assays. The HACEK group (*Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella* species, and *Kingella kingae*) has become a less frequent cause of culture-negative endocarditis because the organisms are more easily detected with contemporary blood culturing systems.

Treatment guidelines for native valve infective endocarditis are listed in Table 47.2.

Valvular endocarditis may be complicated by invasion and destruction of the valve or endocardium or by distant embolization. Large vegetations (>15 mm) increase the risk of embolization. The risk of embolization is greatest before the receipt of appropriate antimicrobials and decreases after the first week of therapy. Large vegetations may occur in patients with delayed diagnosis or infection due to group B streptococci, HACEK, and fungi. Embolization may lead to strokes, mycotic aneurysms, and splenic, hepatic, and renal abscesses. Distant abscesses should be drained before valve replacement surgery. The indications for surgical treatment of endocarditis are listed in Box 47.6.

There is a well-recognized association between *S bovis* bacteremia and carcinoma of the colon or other colonic disease.

KEY FACTS

- ✓ In patients with native valve endocarditis, mitral valve prolapse, bicuspid aortic valves, and aortic sclerosis are the principal predisposing valvular lesions in the absence of prosthetic materials
- ✓ *S bovis* bacteremia and carcinoma of the colon or other colonic disease have a well-recognized association

Prosthetic Valve Endocarditis

Prosthetic valve endocarditis accounts for 1% to 5% of all endocarditis cases. However, the increasing number of patients with prosthetic valves and pacemakers is increasing the population at risk. Prosthetic valve endocarditis can be broadly categorized into early and late onset. Early-onset

Box 47.4 • Definitions of Terminology Used in the Modified Duke Criteria for the Diagnosis of Infective Endocarditis

- Major criteria
    - Blood culture positive for infective endocarditis
        - Typical microorganisms consistent with infective endocarditis from 2 separate blood cultures
            - Viridans group streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus, or*
            - Community-acquired enterococci, in the absence of a primary focus, *or*
        - Microorganisms consistent with infective endocarditis from persistently positive blood cultures, defined as follows:
            - At least 2 positive cultures of blood samples drawn >12 h apart, *or*
            - All of 3 or a majority of ≥4 separate blood cultures, with first and last samples drawn at least 1 h apart
        - Single blood culture positive for *Coxiella burnetii* or anti–phase I immunoglobulin G antibody titer ≥1:800
    - Evidence of endocardial involvement
    - Echocardiogram positive for infective endocarditis (TEE recommended in patients with prosthetic valves, rated at least "possible infective endocarditis" by clinical criteria, or complicated infective endocarditis [paravalvular abscess]; TTE as first test in other patients), defined as follows:
        - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomical explanation, *or*
        - Abscess, *or*
        - New partial dehiscence of prosthetic valve
    - New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)
- Minor criteria
    - Predisposition: predisposing heart condition or injection drug use
    - Fever: >38.0°C (>100.4°F)
    - Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
    - Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor
    - Microbiologic evidence: positive blood culture but not meeting major criteria as noted previously[a] *or* serologic evidence of active infection with organisms consistent with infective endocarditis
    - Echocardiographic minor criteria eliminated

Abbreviations: HACEK, *Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella* species, and *Kingella kingae*; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

[a] Excluding single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.

From Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000 Apr;30(4):633-8; used with permission.

prosthetic valve endocarditis is an infection occurring within 2 months after valve replacement surgery, whereas late-onset prosthetic valve endocarditis occurs more than 2 months postoperatively.

Staphylococci are the leading cause of prosthetic valve endocarditis. The aortic valve is affected more often than the mitral valve. Most early-onset cases are due to infections introduced in the perioperative setting and are caused by staphylococci. In contrast, late-onset cases are frequently due to hematogenous seeding of prosthetic valves from a distant focus of infection. Therefore, the microbiologic nature of late-onset prosthetic valve endocarditis has certain similarities to that of community-acquired native valve endocarditis. Persistent bacteremia, heart failure, abscess formation, and stroke are predictors of a higher death rate in patients with prosthetic valve endocarditis.

Treatment regimens for prosthetic valve endocarditis are summarized in Table 47.3.

Daptomycin therapy at a dosage of 6 mg/kg daily has an efficacy similar to that of standard therapy in *S aureus* bacteremia and endocarditis and causes less nephrotoxicity than β-lactam–based or vancomycin-based regimens. However, longer use of daptomycin is associated with more frequent increases in the creatine kinase level.

Combination therapy with rifampin should be used only in cases of prosthetic valve endocarditis due to staphylococci. Use of rifampin in uncomplicated cases of *S aureus* bacteremia and

Box 47.5 • Common Causes of Culture-Negative Infective Endocarditis

- Administration of antibiotics before obtaining blood cultures
- HACEK group organisms:
  - *Haemophilus* species
  - *Actinobacillus actinomycetemcomitans*
  - *Cardiobacterium hominis*
  - *Eikenella* species
  - *Kingella kingae*
- Nutritionally variant streptococci (*Abiotrophia, Granulicatella,* and *Gemella* species)
- Fungi
- Mycobacteria
- *Coxiella burnetii* (causative agent of Q fever)
- *Chlamydia* species
- *Mycoplasma* species
- *Legionella* species
- *Bartonella* species
- *Tropheryma whipplei*
- *Brucella* species

Abbreviation: HACEK, *Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella* species, and *Kingella kingae*

native valve endocarditis has been associated with prolonging the duration of bacteremia and increased mortality.

Specific Pathogens Causing Endocarditis

Staphylococcus aureus

See the section Health Care–Associated Infections.

Viridans Group Streptococci

These bacteria are part of normal oral and enteric flora. This group is a common cause of subacute bacterial endocarditis, which should be suspected when viridans group streptococci are found in blood cultures. Similar to the pneumococci, they are increasingly likely to show variable resistance to penicillin.

Enterococci

Enterococci are an increasingly important cause of bacterial endocarditis. Enterococci are resistant to many antimicrobial agents, including all cephalosporins. Even for susceptible strains, penicillin or vancomycin monotherapy only inhibits bacterial growth and is not bactericidal. Moreover, strains that are resistant to both the penicillins and vancomycin (vancomycin-resistant enterococci) are spreading worldwide. Linezolid, dalfopristin-quinupristin, and daptomycin are used in cases of vancomycin-resistant enterococci infection. However, these agents are also bacteriostatic and not bactericidal. Of note, dalfopristin-quinupristin is active against only *Enterococcus faecium* and not against *Enterococcus faecalis*.

To achieve the bactericidal activity necessary to cure endocarditis due to enterococci, a combination of penicillin (or ampicillin) plus gentamicin (or streptomycin) is recommended. The choice of aminoglycoside depends on the results of susceptibility testing (Tables 47.3 and 47.4). Four weeks of therapy is adequate for native valve endocarditis that has been present for less than 3 months and is uncomplicated. When a patient is symptomatic for more than 3 months, has a prosthetic heart valve, or is allergic to penicillin—in which case vancomycin needs to be used—6 weeks of therapy is recommended. Vancomycin is considered less effective than penicillin and therefore should be used only in cases of penicillin resistance or if a patient is allergic to penicillin. There is growing evidence that the combination of ceftriaxone and ampicillin is as effective as a β-lactam plus aminoglycoside combination for *E faecalis* native and prosthetic valve endocarditis. A valve replacement procedure may increase the chance of successful treatment in complicated enterococcal endocarditis.

Haemophilus Species Other Than *Haemophilus influenzae*

Haemophilus parainfluenzae, Haemophilus aphrophilus, and *Haemophilus paraphrophilus* are part of the normal oral flora and are members of the HACEK group of organisms. Blood cultures positive for these organisms should raise suspicion for endocarditis. Large valvular vegetations with systemic emboli are frequent with HACEK endocarditis. Treatment of HACEK endocarditis is summarized in Table 47.2.

Echocardiography in Infective Endocarditis

Transesophageal echocardiography is superior to transthoracic echocardiography for the diagnosis and assessment of complications of endocarditis. The sensitivity of transthoracic echocardiography for diagnosing endocarditis is less than 50% in most series, whereas it is more than 95% with transesophageal echocardiography. Moreover, transesophageal echocardiography is superior for detection of cardiac abscesses or mycotic aneurysms, visualization of vegetations less than 5 mm in size, pulmonic valve infection, and vegetation attached to prosthetic valves or cardiac device leads.

Infections of Cardiovascular Implantable Electronic Devices

Permanent pacemakers, implantable cardioverter-defibrillators, and other cardiac devices are being increasingly used. Infections associated with these devices may present as localized generator-pocket infection or systemic infection associated with bacteremia or lead endocarditis. Staphylococci (*S aureus* and CoNS) account for two-thirds of the cases. Regardless of the infecting pathogen and clinical presentation, complete removal of the

Table 47.2 • Treatment of Native Valve Infective Endocarditis

Microorganism	Therapy[a]	Alternative Therapy[a]
Penicillin-sensitive viridans group streptococci and *Streptococcus bovis* (MIC, ≤0.1 mcg/mL)	Aqueous crystalline penicillin G, 12-18×10^6 U/24 h IV either continuously or in 6 equally divided doses for 4 wk *Or* Ceftriaxone sodium 2 g IV or IM for 4 wk[c] *Or* Aqueous penicillin G, 12-18×10^6 U/24 h IV either continuously or in 6 equally divided doses for 2 wk *Plus* Gentamicin sulfate,[d] 1 mg/kg IV or IM every 8 h for 2 wk	Vancomycin,[b] 30 mg/kg IV in 2 equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored for 4 wk Vancomycin therapy is recommended for patients allergic to β-lactams (immediate-type hypersensitivity); serum concentration of vancomycin should be obtained 1 h after completion of the infusion and should be in the range of 30-45 mcg/mL for twice-daily dosing
Relatively penicillin-resistant viridans group streptococci (MIC, >0.1 mcg/mL and <0.5 mcg/mL)	Aqueous crystalline penicillin G, 24×10^6 U/24 h IV either continuously or in 4-6 equally divided doses for 4 wk *Plus* Gentamicin sulfate,[d] 1 mg/kg IV or IM every 8 h for 2 wk	Vancomycin,[b] 30 mg/kg IV in 2 equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored for 4 wk Vancomycin therapy is recommended for patients allergic to β-lactams (immediate-type hypersensitivity); serum concentration of vancomycin should be obtained 1 h after completion of the infusion and should be in the range of 30-45 mcg/mL for twice-daily dosing
Enterococci (gentamicin- or vancomycin-susceptible); all enterococci causing endocarditis must be tested for antimicrobial susceptibility in order to select optimal therapy	Aqueous crystalline penicillin G, 18-30×10^6 U/24 h IV either continuously or in 6 equally divided doses for 4-6 wk *Or* Ampicillin sodium, 12 g/24 h IV either continuously or in 6 equally divided doses *Plus* Gentamicin sulfate,[d] 1 mg/kg IV or IM every 8 h for 4-6 wk (4-wk therapy recommended for patients with symptoms ≤3 mo in duration; 6-wk therapy recommended for patients with symptoms >3 mo in duration) *Or* Ceftriaxone sodium, 2 g/24 h IV or IM in 1 dose for 6 wk *Plus* Ampicillin sodium, 12 g/24 h IV in 6 divided doses for 6 wk	Vancomycin,[b] 30 mg/kg IV in 2 equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored for 4-6 wk *Plus* Gentamicin,[d] 1 mg/kg IV or IM every 8 h for 4-6 wk Vancomycin therapy is recommended for patients allergic to β-lactams (immediate-type hypersensitivity); serum concentration of vancomycin should be obtained 1 h after completion of the infusion and should be in the range of 30-45 mcg/mL for twice-daily dosing Cephalosporins are not acceptable alternatives for patients allergic to penicillin
Penicillin-, aminoglycoside-, and vancomycin-resistant *Enterococcus* species	Linezolid, 1,200 mg/24 h IV or orally in 2 divided doses for >6 wk *Or* Daptomycin 10-12 mg/kg per dose for >6 wk	For patients with endocarditis caused by these strains, treatment should be given in consultation with an infectious diseases specialist Cardiac valve replacement may be necessary for bacteriologic cure. Cure with antimicrobial therapy alone may be <50% Severe, usually reversible thrombocytopenia may occur with use of linezolid, especially after 2 wk of therapy
Staphylococcus aureus[e] methicillin-sensitive	Nafcillin sodium or oxacillin sodium, 2 g IV every 4 h for 6 wk	Cefazolin (or other first-generation cephalosporins in equivalent dosages), 2 g IV every 8 h for 4-6 wk Cephalosporins should be avoided in patients with immediate-type hypersensitivity to penicillin Vancomycin,[b] 30 mg/kg IV in 2 equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored for 6 wk Vancomycin therapy is recommended for patients allergic to β-lactams (immediate-type hypersensitivity); serum concentration of vancomycin should be obtained 1 h after completion of the infusion and should be in the range of 30-45 mcg/mL for twice-daily dosing Daptomycin, 6 mg/kg once daily, may be used as an alternative in right-sided endocarditis due to MSSA or MRSA

Table 47.2 • Continued

Microorganism	Therapy[a]	Alternative Therapy[a]
S aureus[e] methicillin-resistant	Vancomycin,[b] 30 mg/kg IV in 2 equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored for 6 wk *Or* Daptomycin ≥8 mg/kg per dose for 6 wk	Consult an infectious diseases specialist
HACEK group	Ceftriaxone sodium, 2 g IV or IM for 4 wk[c] *Or* Ampicillin sodium 2 g IV every 4 h for 4 wk *Or* Ciprofloxacin 1,000 mg/24 h orally or 800 mg/24 h IV in 2 divided doses if unable to tolerate alternatives *Or* Cefotaxime sodium or other third-generation cephalosporins may be substituted	Consult an infectious diseases specialist
Neisseria gonorrhoeae	Ceftriaxone, 1-2 g every 24 h for ≥4 wk	Aqueous crystalline penicillin G, 20×10^6 U/24 h IV either continuously or in 6 equally divided doses for 4 wk, for penicillin-susceptible isolates
Gram-negative bacilli	Most effective single drug or combination of drugs IV for 4-6 wk	
Urgent empirical treatment for culture-negative endocarditis	Vancomycin,[b] 30 mg/kg IV in 2 equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored for 6 wk *Plus* Gentamicin sulfate,[d] 1.0 mg/kg IV every 8 h for 6 wk	
Fungal endocarditis	Amphotericin B *Plus* Flucytosine (optional) *Plus* Cardiac valve replacement (flucytosine levels should be monitored)	
Suspected *Bartonella*, culture negative	Ceftriaxone sodium, 2 g/24 h IV or IM in 1 dose for 6 wk *Plus* Gentamicin sulfate, 3 mg/kg per 24 h IV or IM in 3 divided doses for 2 wk *With or without* Doxycycline, 200 mg/kg per 24 h IV or orally in 2 divided doses for 6 wk	Consult an infectious diseases specialist

Abbreviations: HACEK, *Haemophilus* spp, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella* spp, and *Kingella kingae*; IM, intramuscularly; IV, intravenously; MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

[a] Dosages recommended are for patients with normal renal function.

[b] Vancomycin dosage should be reduced in patients with impaired renal function. Vancomycin given on an mg/kg basis produces higher serum concentrations in obese patients than in lean patients. Therefore, in obese patients, dosing should be based on ideal body weight. Each dose of vancomycin should be infused over at least 1 hour to reduce the risk of the histamine-releasing red man syndrome.

[c] Patients should be notified that intramuscular injection of ceftriaxone is painful.

[d] Dosing of gentamicin on an mg/kg basis produces higher serum concentrations in obese patients than in lean patients. Therefore, in obese patients, dosing should be based on ideal body weight. (Ideal body weight for men is 50 kg + 2.3 kg per inch taller than 5 feet, and ideal body weight for women is 45.5 kg + 2.3 kg per inch taller than 5 feet.) Relative contraindications to the use of gentamicin are age older than 65 years, renal impairment, or impairment of the eighth nerve. Other potentially nephrotoxic agents (such as nonsteroidal anti-inflammatory drugs) should be used cautiously in patients receiving gentamicin.

[e] For treatment of endocarditis due to penicillin-susceptible staphylococci (MIC, <0.1 mcg/mL), aqueous crystalline penicillin G, 12 to 18×10^6 U/24 hours intravenously either continuously or in 6 equally divided doses for 4 to 6 weeks, can be used instead of nafcillin or oxacillin. Shorter antibiotic courses have been effective in some injection drug users with right-sided endocarditis due to *S aureus*. The routine use of rifampin is not recommended for treatment of native-valve staphylococcal endocarditis.

Data from Wilson WR, Karchmer AW, Dajani AS, Taubert KA, Bayer A, Kaye D, et al; American Heart Association. Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. JAMA. 1995 Dec 6;274(21):1706-13; modified from Steckelberg JM, Guiliani ER, Wilson WR. Infective endocarditis. In: Giuliani ER, Fuster V, Gersh BJ, McGoon MD, McGoon DC, editors. Cardiology: fundamentals and practice. 2nd ed. Vol 2. St. Louis (MO): Mosby Year Book; c1991. p. 1739-72; used with permission of Mayo Foundation for Medical Education and Research; and data from Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015 Oct 13;132(15):1435-1486.

Box 47.6 • Indications for Valve Replacement Surgery in Infective Endocarditis

Heart failure refractory to medical management

One or more systemic embolic episode while receiving appropriate therapy

Perivalvular extension of infection or abscess formation

New electrocardiographic changes suggestive of heart block

Valve dehiscence, rupture, or fistula

Persistent vegetation after systemic embolization

Anterior mitral leaflet vegetation with size >10 mm

Increase in vegetation size despite antimicrobial therapy

Data from Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015 Oct 13;132(15):1435-86.

Table 47.3 • Treatment of Prosthetic Valve Infection

Organism	**Therapy**[a]	**Alternative Therapy/Comments**[a]
Staphylococcus aureus or coagulase-negative staphylococci: methicillin-resistant	Vancomycin,[b] 30 mg/kg IV in 2 equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored for ≥6 wk *Plus* Rifampin,[c] 300 mg orally every 8 h for ≥6 wk *Plus* Gentamicin sulfate,[d] 1 mg/kg IV or IM every 8 h for first 2 wk of therapy. (If organism is not susceptible to gentamicin, ciprofloxacin may be substituted when the organism is susceptible in vitro)	Rifampin increases the amount of warfarin sodium required for antithrombotic therapy
Staphylococcus aureus or coagulase-negative staphylococci: methicillin-susceptible	Nafcillin sodium or oxacillin sodium, 2 g IV every 4 h for ≥6 wk *Plus* Rifampin,[c] 300 mg orally every 8 h for ≥6 wk *Plus* Gentamicin sulfate,[d] 1 mg/kg IV or IM every 8 h for first 2 wk of therapy (if organism is not susceptible to gentamicin, ciprofloxacin may be substituted when the organism is susceptible in vitro)	Rifampin increases the amount of warfarin sodium required for antithrombotic therapy First-generation cephalosporins or vancomycin should be used in patients allergic to β-lactams Cephalosporins should be avoided in patients with immediate-type hypersensitivity to penicillin or to methicillin-resistant staphylococci
Enterococci (gentamicin- or vancomycin-susceptible)	Aqueous crystalline penicillin G, 18-30×10^6 U/24 h IV either continuously or in 6 equally divided doses for 6 wk *Or* Ampicillin sodium, 12 g/24 h IV either continuously or in 6 equally divided doses for 6 wk *Plus* Gentamicin sulfate,[d] 1 mg/kg IV or IM every 8 h for 6 wk	Vancomycin,[b] 30 mg/kg IV in 2 equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored for 4-6 wk *Plus* Gentamicin sulfate,[d] 1 mg/kg IV or IM every 8 h for 4-6 wk Vancomycin therapy is recommended for patients allergic to β-lactams (immediate-type hypersensitivity); serum concentration of vancomycin should be obtained 1 h after completion of the infusion and should be in the range of 30-45 mcg/mL for twice-daily dosing Cephalosporins are not acceptable alternatives for patients allergic to penicillin
Enterococcus faecium	Linezolid, 1,200 mg/24 h IV or orally in 2 divided doses for >6 wk *Or* Daptomycin 10-12 mg/kg per dose for >6 wk	Patients with endocarditis caused by these strains should be treated in consultation with an infectious diseases specialist Cardiac valve replacement may be necessary for bacteriologic cure Cure with antimicrobial therapy alone may be <50% Severe, usually reversible thrombocytopenia may occur with use of linezolid, especially after 2 wk of therapy

Table 47.3 • Continued

Organism	Therapy[a]	Alternative Therapy/Comments[a]
Enterococcus faecalis	Ampicillin sodium, 12 g/24 h IV in 6 divided doses for 4-6 wk *Or* Aqueous penicillin G sodium 18-30 million U/24 h IV continuously or in 6 divided doses for 4-6 wk *Plus* Gentamicin sulfate 3 mg/kg ideal body weight in 2-3 divided doses *Or* Ceftriaxone sodium, 2 g/24 h IV or IM in 1 dose for 6 wk *Plus* Ampicillin sodium, 12 g/24 h IV in 6 divided doses for 6 wk	

Abbreviations: IM, intramuscularly; IV, intravenously.

[a] Dosages recommended are for patients with normal renal function.

[b] Vancomycin dosage should be reduced in patients with impaired renal function. Vancomycin given on an mg/kg basis produces greater serum concentrations in obese patients than in lean patients. Therefore, in obese patients, dosing should be based on ideal body weight. Each dose of vancomycin should be infused over at least 1 hour to reduce the risk of the histamine-releasing red man syndrome.

[c] Rifampin has a unique role in the eradication of staphylococcal infection involving prosthetic material; combination therapy is essential to prevent emergence of rifampin resistance.

[d] Dosing of gentamicin on an mg/kg basis produces greater serum concentrations in obese patients than in lean patients. Therefore, in obese patients, dosing should be based on ideal body weight. (Ideal body weight for men is 50 kg + 2.3 kg per inch over 5 feet, and ideal body weight for women is 45.5 kg + 2.3 kg per inch over 5 feet.) Relative contraindications to the use of gentamicin are age older than 65 years, renal impairment, or impairment of the eighth nerve. Other potentially nephrotoxic agents (such as nonsteroidal anti-inflammatory drugs) should be used cautiously in patients receiving gentamicin.

Data from Wilson WR, Karchmer AW, Dajani AS, Taubert KA, Bayer A, Kaye D, et al; American Heart Association. Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. JAMA. 1995 Dec 6;274(21):1706-13.

Data from Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015 Oct 13;132(15):1435-86.

Table 47.4 • Regimens for a Dental Procedure

		Single Dose 30-60 Min Before Procedure	
Situation	**Agent**	**Adults**	**Children**
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin	2 g IM or IV	50 mg/kg IM or IV
	Or		
	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin[a,b] *Or*	2 g	50 mg/kg
	Clindamycin	600 mg	20 mg/kg
	Or		
	Azithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone[b]	1 g IM or IV	50 mg/kg IM or IV
	Or		
	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

Abbreviations: IM, intramuscularly; IV, intravenously.

[a] Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.

[b] Cephalosporins should not be used in a patient with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.

From Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2007 Oct 9;116(15):1736-54; used with permission.

Box 47.7 • Guidelines for the Diagnosis and Management of Cardiac Device Infections

All patients should have at least 2 blood cultures drawn at initial evaluation

Generator tissue should be obtained for Gram stain and culture, and lead tip tissue should be obtained for culture at device removal

Patients who have blood culture positivity should undergo TEE to assess for device-related endocarditis. Sensitivity of TTE is low, thus it is not the preferred evaluation test for evaluating for device-related endocarditis

All patients with device infection should undergo complete device removal, including all leads, regardless of clinical presentation

Most device leads (even with lead vegetations) can be safely removed percutaneously by experienced operator. Surgical consultation is recommended for lead vegetation >3 cm

Blood cultures should be repeated for all patients after device explantation to document cure of infection and plan for reimplantation of new device

Duration of antimicrobial therapy should also be extended to 4-6 wk in patients with complicated infection (eg, endocarditis, septic venous thrombosis, osteomyelitis, metastatic seeding)

Adequate débridement of generator pocket and control of bloodstream infection should be achieved before reimplantation of a new device

Reevaluation of the continued need for the device should be performed before a new device placement. On average, one-third of patients may no longer need a new device

If an infected cardiac device cannot be removed, then long-term suppressive antibiotic therapy should be administered after completing an initial course of parenteral therapy. Opinion of an infectious diseases expert should be sought for appropriate selection of long-term suppressive therapy

Abbreviations: TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Modified from Sohail MR, Uslan DZ, Khan AH, Friedman PA, Hayes DL, Wilson WR, et al. Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections. J Am Coll Cardiol. 2007 May 8;49(18):1851-9; used with permission.

Box 47.8 • Cardiac Conditions for Which Endocarditis Prophylaxis With Dental Procedures Is Recommended

Prosthetic heart valve

History of infective endocarditis

CHD[a]

1. Unrepaired cyanotic CHD, including palliative shunts and conduits
2. Congenital heart defect completely repaired with prosthetic material or device, whether placed through surgery or catheter intervention, during the first 6 mo after the procedure[b]
3. Repaired CHD with residual defects at or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)

Cardiac transplant recipients who develop valvulopathy

Abbreviation: CHD, congenital heart disease.

[a] Only for these conditions; antibiotic prophylaxis is no longer recommended for any other form of CHD.

[b] Prophylaxis is recommended because endothelialization of prosthetic material occurs within 6 months after the procedure.

From Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2007 Oct 9;116(15):1736-54; used with permission.

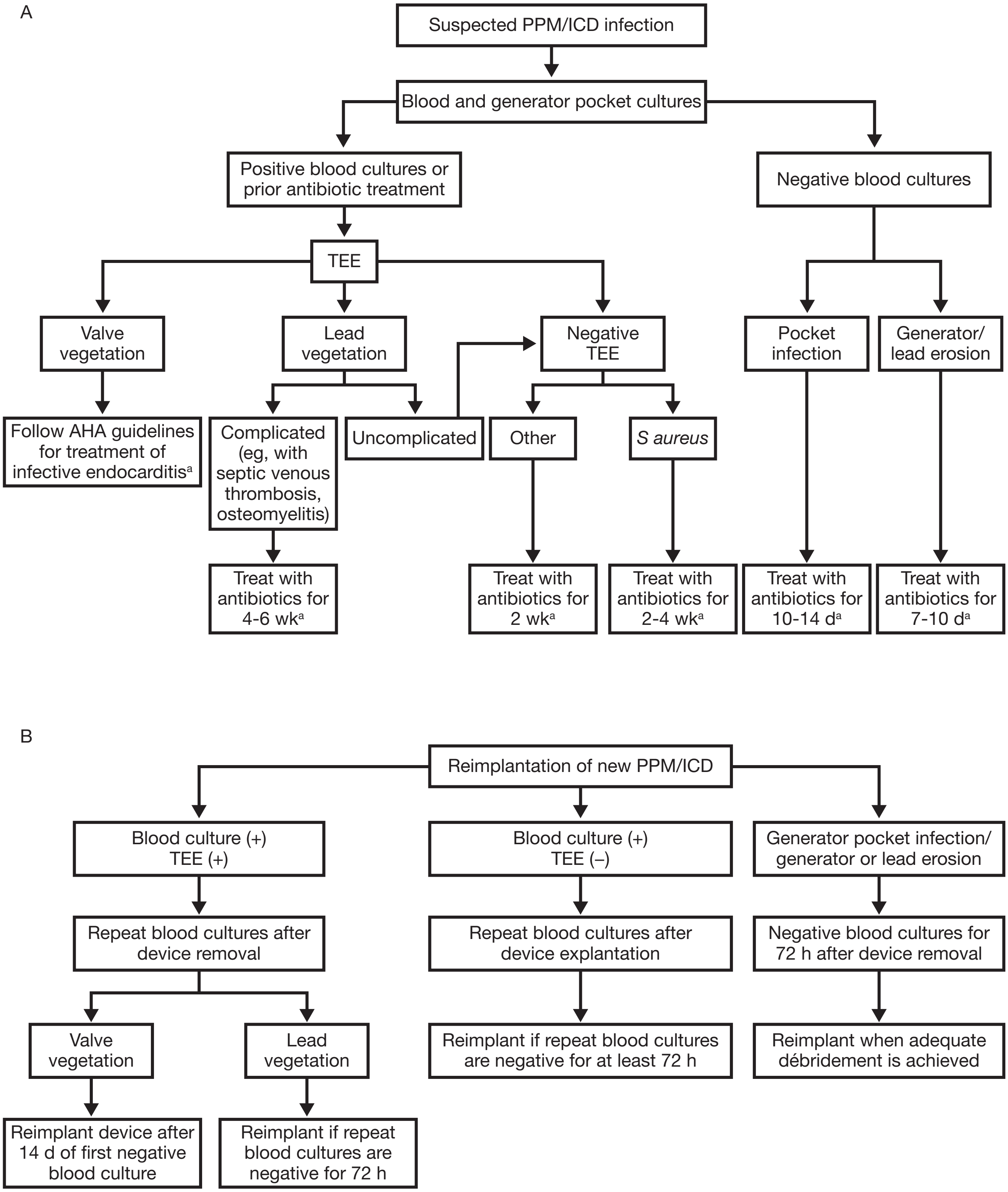
A
Suspected PPM/ICD infection
Blood and generator pocket cultures
Positive blood cultures or prior antibiotic treatment
Negative blood cultures
TEE
Valve vegetation
Lead vegetation
Negative TEE
Pocket infection
Generator/ lead erosion
Follow AHA guidelines for treatment of infective endocarditisa
Complicated (eg, with septic venous thrombosis, osteomyelitis)
Uncomplicated
Other
S aureus
Treat with antibiotics for 4-6 wka
Treat with antibiotics for 2 wka
Treat with antibiotics for 2-4 wka
Treat with antibiotics for 10-14 da
Treat with antibiotics for 7-10 da
B
Reimplantation of new PPM/ICD
Blood culture (+) TEE (+)
Blood culture (+) TEE (–)
Generator pocket infection/ generator or lead erosion
Repeat blood cultures after device removal
Repeat blood cultures after device explantation
Negative blood cultures for 72 h after device removal
Valve vegetation
Lead vegetation
Reimplant if repeat blood cultures are negative for at least 72 h
Reimplant when adequate débridement is achieved
Reimplant device after 14 d of first negative blood culture
Reimplant if repeat blood cultures are negative for 72 h

Figure 47.1. *Algorithm for Management of Cardiac Device Infection. A, Approach to management of infection in adults (also see Box 47.8). This algorithm applies only to patients with complete device explantation. B, Guidelines for reimplantation of new device (also see Box 47.7).* [a] *Duration of antibiotic treatment should be counted from the day of device explantation. AHA indicates American Heart Association; ICD, implantable cardioverter-defibrillator; PPM, permanent pacemaker;* S aureus, Staphylococcus aureus*; TEE, transesophageal echocardiography; +, positive; –, negative.*

(From Sohail MR, Uslan DZ, Khan AH, Friedman PA, Hayes DL, Wilson WR, et al. Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections. J Am Coll Cardiol. 2007 May 8;49[18]:1851-9; used with permission.)

infected device (including generator and transvenous leads) is a requisite for curing these infections.

Box 47.7 and Figure 47.1 summarize Mayo Clinic guidelines for the diagnosis and management of infections of cardiac devices. The American Heart Association endorsed these guidelines in its updated Scientific Statement, published in 2010.

Prevention of Bacterial Endocarditis

Recommendations for the prevention of bacterial endocarditis were extensively revised and simplified in 2007. Endocarditis prophylaxis is no longer recommended before genitourinary or gastrointestinal procedures, regardless of the cardiac lesions. Prophylaxis for infective endocarditis is now recommended only in patients with high-risk cardiac lesions (Box 47.8). For these high-risk patients, prophylaxis is indicated before dental procedures that involve manipulation of the gingival tissue or the periapical region of the teeth or involve perforation of the oral mucosa. Current recommendations for antibiotic prophylaxis before a dental procedure are summarized in Table 47.4.

KEY FACTS

✓ Endocarditis prophylaxis is no longer recommended before genitourinary or gastrointestinal procedures regardless of the cardiac lesions

✓ Prophylaxis for infective endocarditis is now recommended only in patients with high-risk cardiac lesions

48 Pulmonary and Mycobacterial Infections

JENNIFER A. WHITAKER, MD, MS; PRITISH K. TOSH, MD

Viral Infections

Influenza

Influenza causes annual, seasonal epidemics that lead to tens of thousands of deaths each year in the United States. Two influenza A strains (H3N2 and H1N1) and 1 or 2 influenza B strains typically circulate during winter months and undergo minor antigenic mutations (**antigenic drift**) resulting in annual seasonal epidemics. Influenza pandemics occur more rarely (every 20-30 years) and are the result of major antigenic changes (**antigenic shift**) leading to large numbers of infections due to low levels of population immunity. In seasonal epidemics, 80% to 90% of deaths due to influenza occur in persons older than 65 years. Complications include 1) primary influenza pneumonia and 2) secondary bacterial infection, which usually is caused by *Streptococcus pneumoniae, Haemophilus* species, or *Staphylococcus aureus*.

Key Definitions

Antigenic drift: *Minor antigenic mutations that occur during a season.*

Antigenic shift: *Major antigenic mutations that occur and result in pandemics.*

The adamantanes (amantadine and rimantadine) are effective against only the influenza A viruses, not influenza B. However, because levels of adamantane resistance are high in the United States, these medications should not be used for prophylaxis or treatment. Neuraminidase inhibitors (oseltamivir and zanamivir) are effective against disease caused by influenza A and influenza B. Oseltamivir or zanamivir can reduce the duration of symptoms by 1 day when given within 48 hours after symptom onset. Because of seasonal changes in antiviral resistance of circulating strains, recommendations for treatment from the Centers for Disease Control and Prevention should be consulted each year.

KEY FACT

✓ Amantadine and rimantadine are effective against influenza A viruses only. Neuraminidase inhibitors (oseltamivir and zanamivir) are effective against both influenza A and B viruses. When given within 48 hours after symptom onset, both oseltamivir and zanamivir reduce symptom duration by 1 day

Inactivated injectable influenza vaccines are used for disease prevention. Inactivated influenza vaccine is recommended for everyone older than 6 months, but target groups for vaccination include pregnant women, persons older than 50 years, residents

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of long-term care facilities, persons with cardiopulmonary disorders, children older than 6 months who are receiving long-term aspirin therapy (to prevent Reye syndrome), health care personnel, employees of long-term care facilities, providers of home health care, and persons sharing the same household as someone at high risk for influenza. The live attenuated influenza vaccine is no longer recommended for influenza prevention because of its lack of effectiveness. Adverse reactions to influenza vaccines include fever, myalgias, and hypersensitivity. High-dose influenza vaccines are available for adults 65 years or older. Currently, the Centers for Disease Control and Prevention does not specify a preference for high-dose vaccine or standard-dose vaccine for older adults. For persons at high risk for influenza complications who did not receive the vaccine, antiviral prophylaxis can be used for influenza prevention and is effective after exposure to a person with influenza. Post-exposure prophylaxis should be used only when the antiviral can be administered within 48 hours of exposure.

Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) is a common cause of wintertime respiratory illness, especially in children. Lower respiratory tract infection with RSV is uncommon in immunocompetent adults. However, it can be life-threatening in adults who are severely immunocompromised, such as a recipient of a solid-organ transplant or a bone marrow transplant. For these highly immunocompromised adults who have evidence of RSV pneumonia, treatment with oral or inhaled ribavirin with or without intravenous immunoglobulin should be considered.

Adenovirus

Adenovirus can cause viral pneumonia in immunocompetent adults and is classically associated with conjunctivitis and diarrhea. Although usually self-limiting, adenovirus-related lower respiratory tract infections can be severe, and antivirals such as cidofovir should be considered for severe cases or for immunocompromised patients.

KEY FACT

- ✓ Adenovirus can cause viral pneumonia in adults who are immunocompetent and is classically associated with conjunctivitis and diarrhea

Varicella

In adults, varicella (chickenpox) pneumonia is a severe illness. In adults with chickenpox, the most important predictors of varicella pneumonia are cough (which occurs in 25% of patients), profuse rash (macules, vesicles, and pustules in different stages of development), fever for more than 1 week, and age 35 years or older. Early therapy with intravenous acyclovir is recommended for patients at risk for pneumonia.

Cytomegalovirus

Cytomegalovirus (CMV) pneumonia typically occurs in immunocompromised patients, such as those with AIDS who have CD4 counts less than 50/mcL, transplant recipients, and patients with hematologic malignancies. Diffuse, small nodular or hazy infiltrates are seen on chest radiographs of 15% of patients with pneumonia caused by CMV. Interstitial pneumonia due to CMV occurs in 50% of bone marrow graft recipients. Definitive diagnosis of CMV pneumonia is made by finding characteristic inclusion bodies in affected cells, isolating the virus, or detecting CMV antigens or nucleic acids. Isolation of CMV from respiratory tract secretions does not always establish that lung infection is present.

KEY FACTS

- ✓ CMV pneumonia typically occurs in immunocompromised patients
- ✓ CMV pneumonia is diagnosed through finding characteristic inclusion bodies in affected cells, virus isolation, or detection of CMV antigens or nucleic acids
- ✓ CMV isolation from respiratory tract secretions does not always establish the presence of infection

Bacterial Infections

Community-Acquired Pneumonia

Each year in the United States, community-acquired pneumonia (CAP) causes substantial morbidity and mortality among adults, the highest rates being in persons older than 65 years. CAP and influenza combine to be the seventh leading cause of death in the United States. Common microbiologic causes of CAP are *S pneumoniae, Mycoplasma pneumoniae, Haemophilus influenzae, Chlamydophila* (formerly *Chlamydia) pneumoniae, Legionella* species, *S aureus*, and respiratory viruses (most commonly, influenza and RSV) (Table 48.1).

KEY FACT

- ✓ Common microbiologic causes of CAP are *S pneumoniae, M pneumoniae, H influenzae, C pneumoniae, Legionella* species, *S aureus*, and various respiratory viruses (most commonly, influenza and RSV)

The medical unit where a patient receives therapy for CAP is important because unnecessary hospitalizations for this condition increase treatment costs. In addition, patients transferred from a hospital ward to an intensive care unit for CAP care have worse outcomes than those who are admitted directly to the intensive care unit. Although not meant to supplant good clinical judgment, CAP risk stratification indices help clinicians decide the site of care for patients with CAP. The most validated index is the Pneumonia Severity Index, which calculates the risk of death

Table 48.1 • Organisms of Community-Acquired Pneumonia

Organism	Diagnostic Testing	Treatment
Streptococcus pneumoniae	Culture, urine antigen	Penicillins, cephalosporins, respiratory fluoroquinolones
Legionella	Culture on special media, urine antigen	Fluoroquinolones, macrolides
Mycoplasma pneumoniae	Serologic	Fluoroquinolones, macrolides, tetracyclines
Chlamydophila pneumoniae	Serologic	Fluoroquinolones, macrolides, tetracyclines
Moraxella catarrhalis	Culture	Fluoroquinolones, trimethoprim-sulfamethoxazole, amoxicillin-clavulanate
Bordatella pertussis	Polymerase chain reaction or culture	Macrolides
Klebsiella, Enterobacter, and *Serratia*	Culture	Fluoroquinolones, trimethoprim-sulfamethoxazole, fourth-generation cephalosporins, carbapenems
Haemophilus influenzae	Culture	Amoxicillin-clavulanate, cephalosporins, macrolides, or fluoroquinolones

through 20 demographic characteristics, comorbidity, physical examination, and laboratory risk factors. CURB-65, an alternative index, is validated and easier to use (Table 48.2). For a patient in whom CAP is suspected, 1 point is given for each of the following criteria: *c*onfusion, *u*remia (serum urea nitrogen >19 mg/dL), *r*espiratory rate (≥30 breaths per minute), *b*lood pressure (systolic <90 mm Hg or diastolic ≤60 mm Hg), and age of *65* years or more. For patients in whom CAP is suspected but laboratory data are not available, a modified index (CRB-65) can be used. In this index, the uremia risk factor is removed from the calculation.

KEY FACTS

- ✓ CAP risk stratification indices help clinicians decide the location of care for patients with CAP. The Pneumonia Severity Index is the most validated index
- ✓ CURB-65, an alternative index, is validated and easier to use. For a patient suspected to have CAP, 1 point is given for each of the following criteria: *c*onfusion, *u*remia (serum urea nitrogen >19 mg/dL), *r*espiratory rate (≥30 breaths per min), *b*lood pressure (systolic <90 mm Hg or diastolic ≤60 mm Hg), and age *65* years or greater
- ✓ For patients suspected to have CAP who do not have laboratory data available, a modified index (CRB-65) can be used. For its calculation, the uremia risk factor is removed

Table 48.2 • CURB-65 and CRB-65 Severity Scores for Community-Acquired Pneumonia

Clinical Factor	Points
Confusion	1
Serum urea nitrogen >19 mg/dL	1
Respiratory rate ≥30 breaths/min	1
Systolic blood pressure <90 mm Hg or diastolic blood pressure ≤60 mm Hg	1
Age ≥65 y	1
Total points	

Score	Deaths/Total No. of Patients (%)[a]	Recommendation[b]
CURB-65		
0	7/1,223 (0.6)	Low risk; consider home treatment
1	31/1,142 (2.7)	
2	69/1,019 (6.8)	Short inpatient hospitalization or closely supervised outpatient treatment
3	79/563 (14.0)	Severe pneumonia; hospitalize and consider admitting to intensive care unit
4 or 5	44/158 (27.8)	
CRB-65[c]		
0	2/212 (0.9)	Very low risk of death; usually does not require hospitalization
1	18/344 (5.2)	Increased risk of death; consider hospitalization
2	30/251 (12.0)	
3 or 4	39/125 (31.2)	High risk of death; urgent hospitalization

Abbreviations: CRB-65, confusion, respiratory rate, blood pressure, age ≥65 years; CURB-65, confusion, urea nitrogen, respiratory rate, blood pressure, age ≥65 years.

[a] Data are weighted averages from validation studies.[1,2]

[b] Recommendations are consistent with British Thoracic Society guidelines.[3] Clinical judgment may overrule the guideline recommendation.

[c] A CRB-65 score can be calculated by omitting the serum urea nitrogen value, which gives a point range of 0 to 4. This score is useful when blood tests are not readily available.

Modified from Fish D. Pneumonia. In: Mueller BA, Bertch KE, Dunsworth TS, et al, editors. Pharmacotherapy Self-Assessment Program (PSAP). 4th ed. Book 4 (Infectious Diseases). Kansas City (MO): American College of Clinical Pharmacy; c2002. p. 202; used with permission.

1. Aujesky D, Auble TE, Yealy DM, Stone RA, Obrosky DS, Meehan TP, et al. Prospective comparison of three validated prediction rules for prognosis in community-acquired pneumonia. *Am J Med*. 2005;118:384-392.
2. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58:377-382.
3. British Thoracic Society Pneumonia Guidelines Committee. BTS guidelines for the management of community-acquired pneumonia in adults: 2004 update. Available at http://www.brit-thoracic.org.uk/c2/uploads/MACAPrevisedApr04.pdf. Accessed March 20, 2006.

Chest imaging is a requirement for the diagnosis of CAP. Computed tomography is more sensitive than chest radiography, but chest radiography is usually sufficient. The usefulness of other diagnostic tests is controversial because they generally have low yield and infrequently affect clinical care. However, they can be helpful for certain patients and provide data for epidemiologic purposes. Other testing is optional for patients receiving outpatient care for CAP. Pretreatment culture of blood and sputum should be performed for all patients hospitalized with CAP, and urinary antigen testing for *Legionella pneumophila* and *S pneumoniae* should be performed for patients requiring care in an intensive care unit. During influenza season, influenza testing should be performed for all patients with CAP who require hospitalization.

KEY FACTS

- ✓ Chest imaging is required for CAP diagnosis
- ✓ Pretreatment blood and sputum culturing should be performed for all hospitalized patients with CAP. Urinary antigen testing for *Legionella pneumophila* and *S pneumoniae* should be performed for patients with CAP who need treatment in an intensive care unit
- ✓ During influenza season, influenza tests should be performed for all patients with CAP who require hospitalization

Empirical treatment of CAP should be directed toward the suspected pathogens on the basis of a patient's risk factors. Risk factors are summarized in Box 48.1.

KEY FACT

- ✓ Empirical CAP treatment should be directed toward the pathogens suspected on the basis of a patient's risk factors

Box 48.1 • Summary of Risk Factors for Community-Acquired Pneumonia

For previously healthy patients who have not received antimicrobials in the prior 3 mo, reside in locations with <25% macrolide resistance in *Streptococcus pneumoniae*, and will be treated as outpatients, macrolide monotherapy (eg, erythromycin, azithromycin, or clarithromycin) is recommended, and doxycycline is recommended as an alternative

For patients with clinically significant medical comorbidities who have received antimicrobials in the prior 3 mo, have >25% macrolide resistance in *S pneumoniae*, and will be treated as outpatients, treatment options are as follows:

a. A respiratory fluoroquinolone as monotherapy (eg, levofloxacin, moxifloxacin) *or*
b. A β-lactam antibiotic *and* a macrolide *or* doxycycline

For patients with clinically significant medical comorbidities or who have received antimicrobials in the prior 3 mo and will be treated as inpatients, treatment options are as follows:

a. A respiratory fluoroquinolone as monotherapy (eg, levofloxacin, moxifloxacin) *or*
b. A β-lactam antibiotic *and* a macrolide *or* doxycycline

For patients who require disease management in an intensive care unit, recommended treatment is with a β-lactam antibiotic (eg, cefotaxime, ceftriaxone, ampicillin-sulbactam) *and* azithromycin or a respiratory fluoroquinolone (eg, levofloxacin, moxifloxacin)

Empirical treatment of methicillin-resistant *Staphylococcus aureus* with the addition of vancomycin or linezolid should be considered for patients with such clinical risk factors as end-stage renal disease, injection drug use, recent influenza infection, and prior use of antimicrobials, especially fluoroquinolones

If the microbiologic cause of CAP is determined, antimicrobial therapy can be directed toward that pathogen. For hospitalized patients, an intravenously administered antimicrobial can be switched to the oral form when a patient is hemodynamically stable, improving clinically, and able to take medications orally. The oral antimicrobial should be the same agent or of the same drug class as the intravenous antimicrobial.

Guidelines for the treatment of CAP recommend that all but 1 of the following criteria need to occur before stopping antimicrobial therapy: temperature, 37.8°C or less; heart rate, 100 beats per minute or fewer; respiratory rate, 24 breaths per minute or fewer; systolic blood pressure, 90 mm Hg or less; oxygen saturation, 90% or more while breathing room air; ability to take oral medication; and normal mental status. Clinical trials have found that for mild to moderate CAP, shorter courses of therapy (3-5 days) have similar outcomes to longer courses of therapy (7-10 days).

KEY FACTS

- ✓ Before antimicrobial treatment is discontinued in patients with CAP, all but 1 of the following criteria need to occur: temperature, ≤37.8°C; heart rate, ≤100 beats per minute; respiratory rate, ≤24 breaths per minute; systolic blood pressure, ≤90 mm Hg; oxygen saturation, ≥90% while breathing room air; ability to take oral medication; and normal mental status
- ✓ For mild to moderate CAP, shorter courses of therapy (3-5 days) have similar outcomes to longer courses (7-10 days)

Streptococcus pneumoniae (pneumococcus) is a leading cause of community-acquired infections that cause such conditions as pneumonia, meningitis, otitis media, and sinusitis. Similar to many organisms, *S pneumoniae* is becoming increasingly resistant to penicillin. Potential complications of pneumococcal pneumonia include empyema and pericarditis from direct extension of infection. Empyema should be suspected when fever persists despite appropriate antibiotic therapy for pneumococcal pneumonia.

KEY FACT

✓ Empyema, a potential complication of pneumococcal pneumonia, should be suspected when a patient's fever persists despite appropriate antibiotic therapy

Asplenia predisposes to severe infections with *S pneumoniae* (and other encapsulated organisms). After splenectomy, fulminant (purpura fulminans) pneumococcal bacteremia with disseminated intravascular coagulation occurs more commonly and is often fatal. Similarly, *S pneumoniae* infections are more frequent and unusually severe in smokers and patients who have asthma, sickle cell disease, multiple myeloma, alcoholism, HIV infection, or hypogammaglobulinemia.

Two pneumococcal vaccines are available: a polysaccharide vaccine containing the 23 serotypes that most commonly cause pneumococcal infection and a conjugated vaccine containing the 13 serotypes responsible for the most invasive pneumococcal infection. The polysaccharide pneumococcal vaccination is recommended for persons with increased risk of invasive pneumococcal disease or complications, including patients of any age with chronic illness, such as chronic cardiovascular disease (eg, congestive heart failure, cardiomyopathies), chronic pulmonary disease (eg, chronic obstructive pulmonary disease, emphysema), diabetes mellitus, alcoholism, asthma, and chronic liver disease (cirrhosis), and smokers. The following persons should be vaccinated with both the conjugate 13-valent and 23-valent polysaccharide pneumococcal vaccines: persons 65 years or older and adults of any age with cerebrospinal fluid leak, cochlear implants, and immunocompromising conditions (asplenia, AIDS, HIV, malignancy, chronic renal failure, nephrotic syndrome, or transplant recipients). The vaccine can be given simultaneously with influenza virus vaccine. Pneumococcal vaccine booster is recommended at 5 years after the initial dose for high-risk patients with immunocompromising conditions or patients who received the first dose before age 65 years. Immunocompromised patients are recommended to have an initial vaccination with conjugate vaccine followed by booster vaccination with the polysaccharide vaccine a minimum of 8 weeks later. The polysaccharide vaccine is recommended to be given more than 1year after the conjugate vaccine in immunocompetent adults 65 years or older.

Legionella

Legionellae organisms are fastidious gram-negative bacilli. *Legionella pneumophila* causes both CAP and nosocomial pneumonia, typically occurring in summer. Nosocomial legionellosis may be due to contaminated water supplies. Immunocompromised patients, especially those receiving long-term corticosteroid therapy, are especially susceptible to *Legionella* infections. Typical clinical features of legionellosis include weakness, malaise, fever, dry cough, diarrhea, pleuritic chest pain, relative bradycardia, diffuse rales bilaterally, and patchy bilateral pulmonary infiltrates.

Characteristic laboratory features of *Legionella* pneumonia may include decreased sodium and phosphorus values, increased leukocyte level, and increased liver enzyme values. Legionellae organisms will not grow on standard media. Diagnosis depends on assessing the results of special culture, finding organisms by direct fluorescent antibody staining, or detecting an increase in anti-*Legionella* antibody titers. Urine antigen detection is a more sensitive (>80%) and simple diagnostic test for *L pneumophila* infections, but only serogroup 1 is detected.

KEY FACT

✓ Laboratory results characteristic of *Legionella* pneumonia include decreased sodium and phosphorus levels, increased leukocyte count, and increased liver enzyme values

Legionellae organisms are intracellular parasites. As such, they are resistant to all β-lactam drugs and aminoglycosides. Effective agents for treating *Legionella* infection include macrolides, fluoroquinolones, and, to a lesser extent, doxycycline. Fluoroquinolones are considered drugs of choice for therapy. Some authorities recommend adding rifampin for severe infection.

Mycoplasma pneumoniae

Mycoplasma pneumoniae is one of the smallest microorganisms capable of extracellular replication. Because *Mycoplasma* organisms lack a cell wall, the cell-wall–active antibiotics such as penicillins are ineffective for treating *Mycoplasma* infection. Spread by droplet inhalation, *Mycoplasma* infection primarily infects young, previously healthy persons and presents with rapid onset of headache, dry cough, and fever. Results of physical examination are often unremarkable, with the possible exception of bullous myringitis. Chest radiography usually shows bilateral, patchy pneumonitis. The chest radiographic abnormalities are often out of proportion to the physical findings. Pleural effusion is present in 15% to 20% of cases. Neurologic complications include Guillain-Barré syndrome, cerebellar peripheral neuropathy, aseptic meningitis, and mononeuritis multiplex. Hemolytic anemia may occur late in the illness as a result of circulating cold hemagglutinins. Erythema multiforme may also occur. The diagnosis is established through specific complement fixation test. Cold agglutinins are nonspecific and unreliable for diagnosing *Mycoplasma* infections. Fluoroquinolones, macrolides, and tetracyclines are effective therapies. Because immunity to *Mycoplasma* infection is transient, reinfection may occur. Clinical relapse of pneumonia occurs in up to 10% of *Mycoplasma* pneumonia cases.

KEY FACTS

- ✓ *Mycoplasma* infection is spread through droplet inhalation and presents with rapid onset of headache, dry cough, and fever. The organism primarily infects young, previously healthy persons
- ✓ Neurologic complications of *Mycoplasma* infection include Guillain-Barré syndrome, cerebellar peripheral neuropathy, aseptic meningitis, and mononeuritis multiplex
- ✓ Hemolytic anemia may occur late in *Mycoplasma* infection because of circulating cold hemagglutinins, and erythema multiforme may also occur
- ✓ The diagnosis of *Mycoplasma* infection is established with specific complement fixation test. In contrast, cold agglutinins are nonspecific and are not reliable for its diagnosis

Chlamydophila (Chlamydia) pneumoniae

Chlamydophila (Chlamydia) pneumoniae may also cause so-called atypical pneumonia. *Chlamydia trachomatis* and *Chlamydophila psittaci* are the other 2 chlamydial species that cause human disease. In young adults, *C pneumoniae* causes 10% of pneumonia cases and 5% of bronchitis cases. It has caused community outbreaks, and nosocomial transmission has occurred. Half of US adults are seropositive for *C pneumoniae*. Birds are the source of infection with *C psittaci* (psittacosis), but no animal reservoir exists for *C pneumoniae*. Clinical manifestations of infection are usually mild and may resemble those caused by *M pneumoniae*. Pharyngitis occurs 1 to 3 weeks before the onset of pulmonary symptoms, and cough may last for weeks. The diagnosis is based on serologic testing. Treatment is with a fluoroquinolone, doxycycline, or a macrolide. Of note, trimethoprim-sulfamethoxazole and β-lactam antibiotics such as penicillins and cephalosporins are not active against chlamydial species.

Moraxella

Moraxella catarrhalis (formerly called *Branhamella catarrhalis*) is a respiratory tract pathogen primarily causing bronchitis and pneumonia in persons with chronic obstructive pulmonary disease. It also can cause otitis media, sinusitis, meningitis, bacteremia, and endocarditis in immunosuppressed patients. Ampicillin resistance through β-lactamase production is common. Trimethoprim-sulfamethoxazole, the fluoroquinolones, and amoxicillin-clavulanate are effective for therapy.

Bordetella pertussis

Bordetella pertussis infection often results in persistent coughing in older children and adults, and it is potentially fatal in infants. Whooping cough may cause severe lymphocytosis (>100 lymphocytes ×10^9/L).

KEY FACT

- ✓ *Bordetella pertussis* infection often causes persistent coughing in older children and adults, and it is potentially fatal in infants. Whooping cough can cause severe lymphocytosis

Diagnosis of *B pertussis* infection may be difficult. Molecular testing (polymerase chain reaction) of a nasopharyngeal aspirate is more sensitive, rapid, and reliable than cultures. Early treatment of pertussis with a macrolide (erythromycin, clarithromycin, or azithromycin) is recommended. The duration of pertussis treatment is 14 days for the patient and 5 days for persons in close contact with affected patients for prevention, irrespective of age or vaccination status. Aerosolized bronchodilators or corticosteroids may alleviate the persistent coughing. A pertussis-containing tetanus-diphtheria vaccine is recommended for use in adults. It is given as a single booster to replace a dose of tetanus-diphtheria booster. This approach is particularly emphasized for adults who have close contact with infants (eg, parents, health care workers, day care providers). Women should receive a pertussis-containing tetanus-diphtheria vaccination after 20 weeks' gestation for each pregnancy.

KEY FACT

- ✓ Early treatment of pertussis with the macrolides erythromycin, clarithromycin, or azithromycin is recommended. Treatment duration is 14 days for the patient with pertussis and 5 days for persons who have been in close contact with pertussis-affected patients, irrespective of age or vaccination status

Klebsiella, Enterobacter, and *Serratia*

Klebsiella pneumoniae is an important cause of both CAP and nosocomial pneumonia and often is associated with alcoholism, diabetes mellitus, and chronic obstructive pulmonary disease. Sputum the color of red currant jelly is a characteristic sign. Lung abscess and empyema are more frequent with *K pneumoniae* than with other pneumonia-causing organisms, especially in persons with alcoholism. Third-generation cephalosporins are the drugs of choice for treating most types of *Klebsiella*. Strains of *Klebsiella* have emerged that are resistant to ceftazidime. This resistance is caused by an extended-spectrum β-lactamase. Susceptibility testing results for such strains may erroneously report that they are susceptible to cefotaxime. If the strains are resistant to ceftazidime, they should be considered resistant to all cephalosporins. Resistance to carbapenem antibiotics through *K pneumoniae* carbapenemases has also emerged; treatment with such antimicrobials as aminoglycosides and colistin may be needed for these organisms.

KEY FACTS

✓ *Klebsiella pneumoniae* is an important cause of CAP and nosocomial pneumonia and often is associated with alcoholism, diabetes mellitus, and chronic obstructive pulmonary disease

✓ Sputum the color of red currant jelly is a characteristic sign of *K pneumoniae* infection. Lung abscess and empyema are more frequent with *K pneumoniae* than with other pneumonia-causing organisms, especially in persons with alcoholism

Enterobacter and *Serratia* are primarily associated with nosocomial infections. *Enterobacter* species, such as *Enterobacter cloacae* and *Enterobacter aerogenes*, are often resistant to third-generation cephalosporins, such as cefotaxime. Despite in vitro data suggesting the susceptibility of *Enterobacter* and *Serratia*, β-lactamase production is induced when they are grown in the presence of cephalosporins. Carbapenems, such as imipenem or meropenem, fluoroquinolones, cefepime, and trimethoprim-sulfamethoxazole, are usually active against these strains.

Nocardia **Pneumonia**

Nocardia asteroides, Nocardia brasiliensis, and *Nocardia otitidiscaviarum* can cause pneumonia in susceptible persons. *Nocardia asteroides* is a weakly acid-fast saprophytic bacterium present in soil, dust, plants, and water. Infection is more common among immunosuppressed patients. Primary infection leads to necrotizing pneumonia with abscess formation. Pulmonary nodules suggestive of cancer metastases and dense alveolar infiltrates are common chest radiographic findings. *Nocardia* infection may produce pleural effusion. Lymphohematogenous spread occurs in 20% of affected patients; in nearly all of these patients, a brain abscess develops.

Isolation of the *Nocardia* organism from the sputum of immunocompetent patients might represent colonization because the saprophytic state is well recognized. However, in an immunocompromised patient, this colonization should be considered a true infection. Most *Nocardia* isolates are susceptible to trimethoprim-sulfamethoxazole. Nevertheless, use of an initial combination therapy with the addition of imipenem, ceftriaxone, or amikacin should be considered in severe or complicated cases.

Aspiration Pneumonia

Aspiration pneumonia can be acute or chronic. The acute type usually results from aspiration of a liquid volume larger than 50 mL and with a pH less than 2.4. The aspiration produces classic aspiration pneumonia that is often sterile; the role of antibiotics in the absence of supporting cultures is unclear and controversial. Predisposing factors include use of a nasogastric tube, anesthesia, coma, seizures, central nervous system problems, diaphragmatic hernia with reflux, and tracheoesophageal fistula. Nosocomial aspiration pneumonia is caused by *Escherichia coli, S aureus, K pneumoniae, Pseudomonas aeruginosa,* and anaerobic organisms. Community-acquired aspiration pneumonias are caused by infections due to anaerobes. Preventive measures are important for patients with the identified predisposing factors.

Chronic aspiration pneumonia results from recurrent aspiration of small volumes. Examples include patients with reflux aspiration who have granuloma caused by mineral oil. Symptoms include chronic cough, patchy lung infiltrates, and nocturnal wheeze.

Lung Abscess

Lung abscess is a circumscribed collection of pus in the lung that leads to cavity formation; the cavity has an air-fluid level on chest radiography. Lung abscess usually is caused by bacteria, particularly anaerobic bacilli (30%-50% of cases), aerobic gram-positive cocci (25%), and aerobic gram-negative bacilli (5%-12%). Polymicrobial infections are the most common causes of lung abscess. Suppuration leading to lung abscess can result from primary, opportunistic, and hematogenous lung infection. Primary lung abscess is caused by oral infection; aspiration accounts for up to 90% of all abscesses. Alcohol abuse and dental caries also contribute. Lung abscesses caused by opportunistic infections occur in elderly patients with a blood dyscrasia and in patients with cancer of the lung or oropharynx. In patients with advanced HIV infection, lung abscess can develop in association with a broad spectrum of pathogens, including opportunistic organisms. These patients have a poor prognosis.

KEY FACT

✓ Primary lung abscess is caused by oral infection. Aspiration accounts for up to 90% of all abscesses, and alcohol abuse and dental caries also contribute

Hematogenous lung abscesses occur with septicemia, septic embolism, and sterile infarcts (3% of cases). A history of any of these conditions in association with fever, cough with purulent or bloody sputum, weight loss, and leukocytosis suggests the diagnosis. Chest radiography may show cavitated lesions. The abscess may rupture into the pleural space and cause empyema. Bronchoscopy may be necessary to obtain samples for culture, to drain the abscess, and to exclude obstructing lesions. High morbidity and mortality rates (20%) are associated with lung abscess despite antibiotic therapy. The prognosis is worse for patients with a large abscess and those infected with *S aureus, K pneumoniae*, and *P aeruginosa*. Treatment includes drainage (physiotherapy, postural, and bronchoscopic) and antibiotic therapy (including coverage for anaerobic organisms) for 4 to 6 weeks. Surgical treatment is usually needed only if medical therapy fails.

KEY FACTS

- ✓ High morbidity and mortality rates (20%) are associated with lung abscess despite antibiotic treatment. The prognosis is worse for patients with a large abscess and those with *S aureus, K pneumoniae*, and *P aeruginosa* infections
- ✓ Treatment includes physiotherapy, postural, and bronchoscopic drainage; antibiotic therapy for 4 to 6 weeks; and surgical treatment if medical therapy fails

Mycobacterial Infections

Mycobacterium tuberculosis

Worldwide, *Mycobacterium tuberculosis* causes the most common type of human-to-human chronic infection due to mycobacteria. The most common mode of transmission is inhalation of droplet nuclei. Of persons exposed to *M tuberculosis*, 30% become infected. Among infected persons, active primary disease occurs in less than 5%; active disease from reactivation develops in less than 5%. Active infection is diagnosed through documenting *M tuberculosis* in clinical specimens. Sputum and gastric washings have an approximately 30% diagnostic yield. Bronchoscopy with bronchoalveolar lavage has a 40% diagnostic yield, which increases to almost 95% with biopsy. Culture of pleural fluid alone has a low sensitivity, but culture of pleural biopsy specimens has a 70% diagnostic yield. Faster culture results are available with broth culture systems (results within 1.5-2 weeks) and nucleic acid amplification (results within 8 hours). **Latent tuberculosis (TB) infection** is the current term for the condition in a person who is infected with *M tuberculosis* (positive purified protein derivative [PPD] skin test) but does not have active tuberculosis.

Key Definition

Latent tuberculosis infection: ***The condition of M tuberculosis infection (positive purified protein derivative skin test) without active tuberculosis.***

The result of a PPD tuberculin skin test can be positive within 4 weeks after exposure to *M tuberculosis* (TB). The result is negative in 25% of patients who have active TB. The PPD result can be false-negative when the following factors are present: concomitant infections with viruses or bacteria, receipt of live virus vaccinations, chronic renal failure, nutritional deficiency, lymphoid malignancies, leukemias, corticosteroid and immunosuppressive drug therapies, newborn or elderly patients, recent or overwhelming infection with mycobacteria, and acute stress. The annual risk of active TB for those who have a positive result on PPD skin testing depends on the underlying medical condition. The risk is particularly high in persons living with HIV (annual risk, 8%-10%) and in recent test converters (2%-5%). PPD skin testing should use a 5-tuberculin-unit preparation; the widest induration is read at 48 and 72 hours. Prior vaccination with bacille Calmette-Guérin (BCG) is not a contraindication for the PPD test. However, when there is concern that the PPD test result might be related to prior infection with BCG, an interferon gamma release test may be performed for further clarification. Large PPD reactions (≥20 mm) are not likely caused by BCG. The classification of PPD test results is summarized in Table 48.3.

KEY FACTS

- ✓ PPD skin testing should be done with a 5-tuberculin-unit preparation; the widest induration is read at 48 and 72 hours
- ✓ Prior vaccination with BCG is not a contraindication for the PPD test. No diagnostic method can reliably distinguish positive PPD skin test results caused by BCG vaccination from those caused by mycobacterial infections, although large reactions (≥20 mm) are not likely caused by BCG

The role of the serum interferon-γ release assay continues to evolve and has the promise of increased specificity of testing to identify latent TB. This assay may help distinguish latent TB infection from nontuberculous mycobacterial infection and BCG vaccination. Current Centers for Disease Control and Prevention guidelines suggest that the assay may be used in all circumstances in which the PPD skin test is used. Compared

Table 48.3 • Targeted Tuberculin Testing for Latent TB Infection: Classification

Positive Reaction, by mm of Induration		
≥5	**≥10**	**≥15**
HIV-infected persons Persons in recent contact with persons who have active TB Persons with fibrotic changes on chest radiography consistent with prior TB infection Patients with organ transplants Persons who are immunosuppressed for other reasons (eg, taking the equivalent of >15 mg/d of prednisone for ≥1 mo, taking TNF-α antagonists)	Recent (<5 y) immigrants from high-prevalence countries Injection drug users Residents of and employees at high-risk congregate settings Mycobacteriology laboratory personnel Persons with clinical conditions that place them at high risk Children <4 y of age Infants, children, and adolescents exposed to adults in high-risk categories	Any person, including persons with no known risk factors for TB infection. However, targeted skin testing programs should be conducted only among high-risk groups

Abbreviations: TB, tuberculosis; TNF-α, tumor necrosis factor α.

Modified from American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR Recomm Rep. 2000 Jun 9;49(RR-6):1-51.

with the PPD skin test, the assay is probably less subject to reader bias and error, requires only a single health care visit, and is less likely to be positive after BCG vaccination. Like the PPD skin test, the assay result may be negative in patients who have active TB.

KEY FACTS

✓ The serum interferon-γ release assay may help distinguish latent tuberculous infection from nontuberculous mycobacterial infection and BCG vaccination

✓ Compared with the PPD skin test, the serum interferon-γ release assay is probably less subject to reader bias and error, requires a single health care visit, and is less likely to be positive after BCG vaccination. Similar to the PPD skin test, the assay result may be negative for patients with active TB

In the United States, 4% of all patients with TB have pleural involvement, and pleural TB constitutes 23% of the extrapulmonary TB cases. Effusions usually occur 3 to 6 months after the primary infection. Acute presentation (cough, fever, and pleuritic chest pain) is more common in younger patients than older ones. Bilateral exudative effusions occur in up to 8% of patients, and the PPD skin test is positive in more than 66%. The effusions typically have high protein levels (>5 g/dL), lymphocytosis (>50% of the total white blood cell count), and low glucose levels (<50 mg/dL). A low pleural fluid pH occurs in 20% of patients who have pleural TB. Pleural biopsy specimens show caseous granulomas in up to 80% of patients, and cultures of biopsy specimens are positive in more than 75%. Cultures of pleural fluid are positive in only 20% to 40% of patients, and sputum is positive in 40%. Bronchopleural fistula is a complication of biopsy in pleural TB.

Miliary TB constitutes 10% of cases of extrapulmonary TB. It is clinically characterized by the diffuse presence of small (<2 mm) nodules throughout the body. The spleen, liver, and lung are frequently involved. The disease can be acute and fatal or insidious in onset and slowly progressive. Chest radiography shows typical miliary lesions in more than 65% of patients. Among patients with miliary TB, sputum smear microscopy findings are negative in up to 80%, and the PPD skin test is negative in approximately 50%.

Tuberculous lymphadenitis (ie, scrofula) is the most common form of extrapulmonary TB. It is more common in children and young adults than in older persons. Cervical lymph nodes are affected most commonly. Skeletal TB is becoming less common; when identified, it is more common in young than in older adults. Any bone can be involved, but the vertebrae are involved in 50% of skeletal TB cases. Pott disease is tuberculous spondylitis and may produce severe kyphosis. Tuberculous meningitis is the most common form of central nervous system involvement and is localized mainly to the base of the brain. It occurs more commonly in immunocompromised patients. Tuberculous meningitis is often insidious in onset.

Therapy is indicated for all patients with culture-positive TB. Treatment for drug-susceptible TB includes 4-drug therapy for 2 months of initiation and 2-drug therapy for an additional 4 months of the continuation phase (Tables 48.4 and 48.5; Figures 48.1 and 48.2). With strictly administered 6-month regimens, more than 90% of patients have negative smear results after 2 months of therapy, more than 95% are cured, and less than 5% have relapse. A 9-month regimen provides a cure rate higher than 97% and a relapse rate less than 2%. All treatment programs should be recommended and preferably undertaken by physicians and health care workers experienced in the management

Table 48.4 • Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

Initial Phase			Continuation Phase				Rating[a] (Evidence)[b]	
Regimen	**Drugs**	**Interval and Doses[c] (Minimal Duration)**	**Regimen**	**Drugs**	**Interval and Doses[c,d] (Minimal Duration)**	**No. of Total Doses, Range (Minimal Duration)**	**HIV Negative**	**HIV Positive**
1	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk) *or* 5 d/wk for 40 doses (8 wk)[e]	1a	INH and RIF	7 d/wk for 126 doses (18 wk) *or* 5 d/wk for 90 doses (18 wk)[e]	182-130 (26 wk)	A (I)	A (II)
			1b	INH and RIF	Twice weekly for 36 doses (18 wk)	92-76 (26 wk)	A (I)	A (II)[f]
			1c[g]	INH and RPT	Once weekly for 18 doses (18 wk)	74-58 (26 wk)	B (I)	E (I)
2	INH RIF PZA EMB	7 d/wk for 14 doses (2 wk), *then* twice weekly for 12 doses (6 wk) *or* 5 d/wk for 10 doses (2 wk)[e], *then* twice weekly for 12 doses (6 wk)	2a	INH and RIF	Twice weekly for 36 doses (18 wk)	62-58 (26 wk)	A (II)	B (II)[f]
			2b[g]	INH and RPT	Once weekly for 18 doses (18 wk)	44-40 (26 wk)	B (I)	E (I)
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 wk)	3a	INH and RIF	3 times weekly for 54 doses (18 wk)	78 (26 wk)	B (I)	B(II)
4	INH RIF EMB	7 d/wk for 56 doses (8 wk) *or* 5 d/wk for 40 doses (8 wk)[e]	4a	INH and RIF	7 d/wk for 217 doses (31 wk) *or* 5 d/wk for 155 doses (31 wk)[e]	273-195 (39 wk)	C (I)	C (II)
			4b	INH and RIF	Twice weekly for 62 doses (31 wk)	118-102 (39 wk)	C (I)	C (II)

Abbreviations: EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; RPT, rifapentine.

[a] Definitions of ratings: A, preferred; B, acceptable alternative; C, offer when A and B cannot be given; E, should never be given.

[b] Definitions of evidence: I, randomized clinical trial; II, data from clinical trials that were not randomized or were conducted in other populations; III, expert opinion.

[c] When directly observed therapy is used, drugs may be given 5 days weekly and the necessary number of doses adjusted accordingly. Although no studies have compared 5 daily doses with 7 daily doses, extensive experience indicates this regimen would be an effective practice.

[d] Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive therapy for a 7-month continuation phase (31 weeks; either 217 doses [daily] or 62 doses [twice weekly]).

[e] Drugs given for 5 days weekly are always given through directly observed therapy. Rating for these regimens is A (III).

[f] Not recommended for HIV-infected patients with CD4+ cell counts <100/mcL.

[g] Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at completion of 2 months of therapy and do not have cavitation on initial chest radiograph. For patients receiving this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

From Blumberg HM, Burman WJ, Chaisson RE, Daley CL, Etkind SC, Friedman LN, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med. 2003 Feb 15;167(4):603-62; used with permission.

of mycobacterial diseases. The most important impediment to lack of adequate therapy worldwide is the lack of adherence to the treatment. Cavitary TB should be treated for 9 months (7 months of continuation phase) if sputum cultures are positive after 2 months of induction therapy. Extrapulmonary TB can be treated effectively with a 6- or 9-month regimen. However, miliary TB, bone and joint TB, and tuberculous meningitis in infants and children may require treatment for 12 months or more.

KEY FACT

✓ Therapy is indicated for patients with culture-positive TB. It usually should include multidrug therapy (>2 drugs at a minimum; 4-drug treatment is recommended) for patients with active TB

Table 48.5 • First-Line Drug Therapies for Tuberculosis[a,b]

	Dose, mg/kg							
	Daily		2 Times Weekly[c]		3 Times Weekly[c]			
Drug	Children[d]	Adults	Children[d]	Adults	Children[d]	Adults	Adverse Reactions	Monitoring
INH[e] (maximal dose in mg)	10-20 (300)	5 (300)	20-40 (900)	15 (900)	20-40 (900)	15 (900)	Increased liver enzyme level, hepatitis, peripheral neuropathy, mild effects on central nervous system, drug interactions	Baseline measurements of liver enzymes for adults Repeat measurements when baseline results are abnormal, when patient is at high risk for adverse reactions, or when patient has symptoms of adverse reactions
RIF[f] (maximal dose in mg)	10-20 (600)	10 (600)	10-20 (600)	10 (600)	10-20 (600)	10 (600)	GI upset, drug interactions, hepatitis, bleeding problems, flulike symptoms, rash	Baseline measurements for adults: CBC, platelets, liver enzymes Repeat measurements when baseline results are abnormal or when patient has symptoms of adverse reactions
PZA[g] (maximal dose in mg)	15-30 (2,000)	15-30 (2,000)	50-70 (4,000)	50-70 (4,000)	50-70 (3,000)	50-70 (3,000)	Hepatitis, rash, GI upset, joint aches, hyperuricemia, gout (rare)	Baseline measurements for adults: uric acid, liver enzymes Repeat measurements when baseline results are abnormal or when patient has symptoms of adverse reactions
EMB[h]	15-25	15-25	50	50	25-30	25-30	Optic neuritis	Baseline and monthly tests: visual activity, color vision
SM[i] (maximal dose in mg)	20-40 (1,000)	15 (1,000)	25-30 (1,500)	25-30 (1,500)	25-30 (1,500)	25-30 (1,500)	Ototoxicity (hearing loss or vestibular dysfunction), renal toxicity	Baseline and repeat as needed: hearing, kidney function

Abbreviations: CBC, complete blood cell count; EMB, ethambutol; GI, gastrointestinal tract; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; SM, streptomycin.

[a] Adjust weight-based dosages as patient's weight changes.

[b] INH, RIF, PZA, and EMB are administered orally; SM is administered intramuscularly.

[c] Directly observed therapy should be used with all regimens administered 2 or 3 times weekly.

[d] Age less than 12 years.

[e] Hepatitis risk increases with age and alcohol consumption. Pyridoxine can prevent peripheral neuropathy.

[f] Severe interactions with methadone, oral contraceptives, and many other drugs. Drug colors the body fluids orange and may permanently discolor soft contact lenses.

[g] Treat hyperuricemia only when patient has symptoms.

[h] Not recommended for children too young to be monitored for changes in vision, unless tuberculosis is drug-resistant.

[i] Avoid or decrease dose in adults older than 60 years.

Data from American Thoracic Society; CDC; Infectious Diseases Society of America. Treatment of tuberculosis. MMWR Recomm Rep. 2003 Jun 20;52(RR-11):1-77. Erratum in: MMWR Recomm Rep. 2005 Jan 7;53(51):1203. Dosage error in article text.

Drug-resistant TB is an increasingly recognized problem. Drug resistance can develop against a single first-line drug. Multidrug-resistant TB refers to resistance that develops to at least both isoniazid and rifampin. Extensively drug-resistant TB is defined as resistance to at least both isoniazid and rifampin and resistance to fluoroquinolones or aminoglycosides.

Treatment of latent TB infection is indicated for persons with a positive PPD skin test result who do not have active infection. When latent TB infection is likely caused by an isoniazid-sensitive organism, treatment options include isoniazid at a dose of 300 mg daily or 900 mg biweekly. Pyridoxine is usually added to prevent peripheral neuropathy, which is particularly common

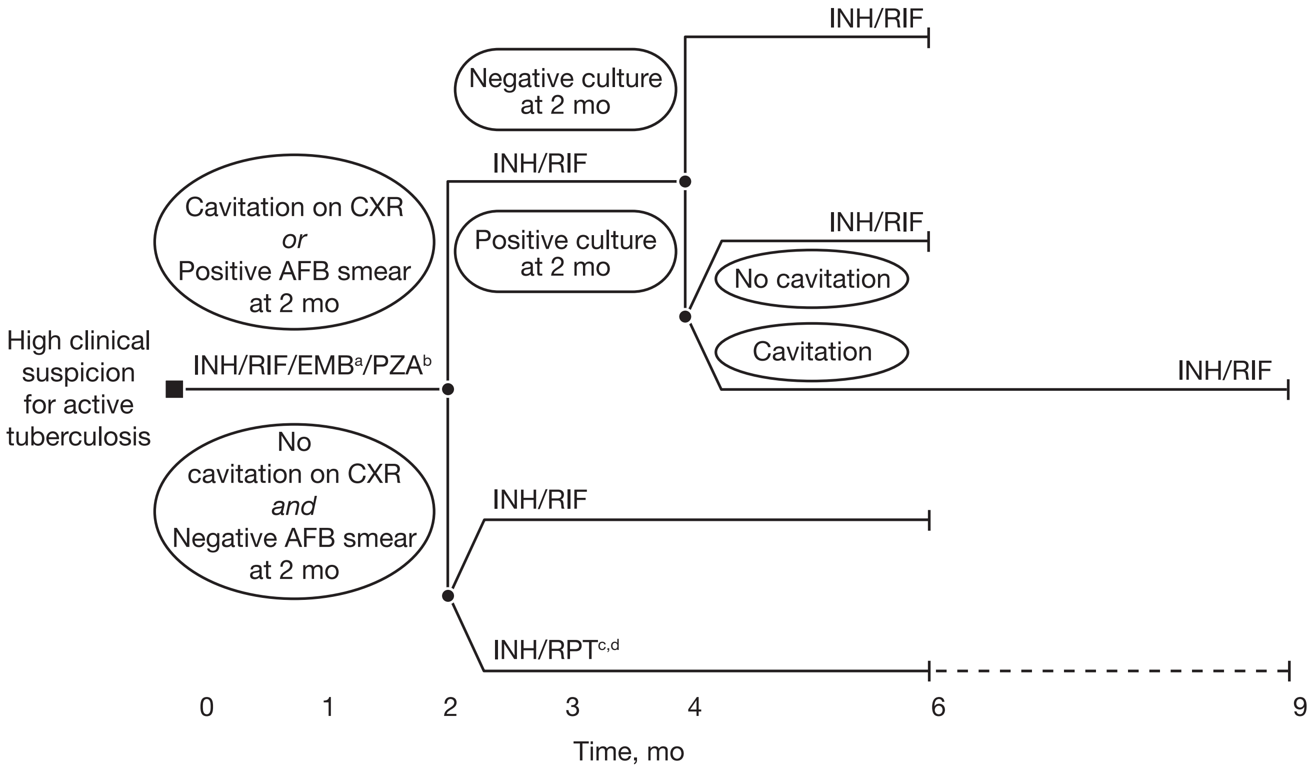

Figure 48.1. *Treatment Algorithm for Tuberculosis (TB). Patients in whom TB is proved or strongly suspected should have treatment initiated with isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) for the first 2 months. Another acid-fast bacilli (AFB) smear and culture should be performed after 2 months of treatment. If cavities were seen on initial chest radiograph (CXR) or the AFB smear is positive at completion of 2 months of treatment, the continuation phase of treatment should consist of INH and RIF daily or twice weekly for 4 months (total, 6 months of treatment). If cavitation was present on initial CXR and if the culture at completion of 2 months of therapy is positive, the continuation phase should be lengthened to 7 months (total, 9 months of treatment). If the patient has HIV infection and a CD4+ cell count less than 100/mcL, the continuation phase should consist of daily or 3-times-weekly doses of INH and RIF. For patients without HIV infection who have no cavitation on CXR and negative AFB smears at completion of 2 months of treatment, the continuation phase may consist of either once-weekly doses of INH and rifapentine (RPT) or daily or twice-weekly doses of INH and RIF (total of 6 months) (bottom of figure). Patients receiving INH and RPT and whose 2-month cultures are positive should have treatment extended by 3 additional months (total, 9 months of treatment).* [a] *Use of EMB may be discontinued when results of drug susceptibility testing indicate no drug resistance.* [b] *Use of PZA may be discontinued after 2 months (56 doses).* [c] *RPT should not be used for HIV-infected patients with TB or patients with extrapulmonary TB.* [d] *Therapy should be extended to 9 months if the 2-month culture is positive.*

(From Blumberg HM, Burman WJ, Chiasson RE, Daley CL, Etkind SC, Friedman LN, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med. 2003 Feb 15;167[4]:603-62; used with permission.)

in patients with diabetes mellitus, alcohol abuse, or kidney disease. Rifampin (600 mg daily) is an alternative option. The recommended duration for therapy of latent TB infection is 6 to 9 months with isoniazid. Rifampin is typically given for 4 months; isoniazid and rifapentine for 12 weekly doses that must be administered by directly observed therapy.

KEY FACT

✓ Treatment of latent TB infection is indicated for persons with a positive PPD skin test result who do not have active infection

Nontuberculous Mycobacteria

Mycobacteria other than *M tuberculosis* and *Mycobacterium leprae* are commonly classified as *nontuberculous mycobacteria* (NTM), even though tubercle formation occurs. Most NTMs have been isolated from natural water and soil. Human-to-human spread has not been documented.

Chronic pulmonary disease is caused most frequently by *Mycobacterium avium* complex and *Mycobacterium kansasii*. Pulmonary disease is more common in older adults, persons with underlying chronic obstructive pulmonary disease, smokers, persons who abuse alcohol, and some children with cystic fibrosis. Most of these patients (>90%) have bronchiectasis or small nodules without predilection for any lobe.

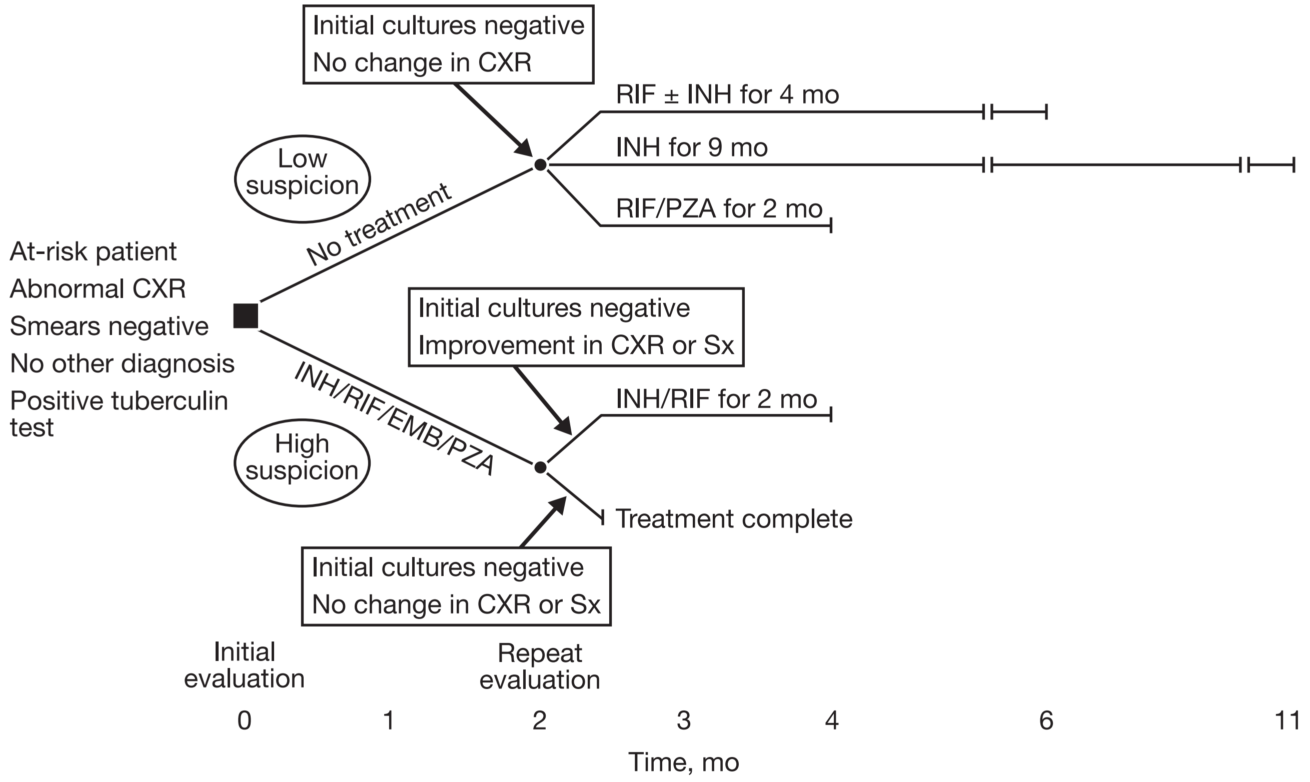
Initial cultures negative
No change in CXR
RIF ± INH for 4 mo
INH for 9 mo
RIF/PZA for 2 mo
Low suspicion
No treatment
At-risk patient
Abnormal CXR
Smears negative
No other diagnosis
Positive tuberculin test
Initial cultures negative
Improvement in CXR or Sx
INH/RIF/EMB/PZA
INH/RIF for 2 mo
High suspicion
Treatment complete
Initial cultures negative
No change in CXR or Sx
Initial evaluation
Repeat evaluation
0
1
2
3
4
6
11
Time, mo

Figure 48.2. *Treatment Algorithm for Active, Culture-Negative Pulmonary Tuberculosis (TB) and Inactive TB. The decision to begin treatment of a patient with sputum smears that are negative depends on the degree of clinical suspicion that the patient has TB. If suspicion is high (bottom of figure), multidrug therapy should be initiated before acid-fast smear and culture results are known. If the diagnosis is confirmed by a positive culture, treatment can be continued to complete a standard course of therapy (see Figure 48.1). If initial cultures continue to be negative and treatment has consisted of multiple drugs for 2 months, 2 options are available depending on reevaluation at 2 months (bottom of figure): 1) If the patient shows symptomatic or radiographic improvement without another apparent diagnosis, a diagnosis of culture-negative TB can be inferred. Treatment should be continued with isoniazid (INH) and rifampin (RIF) alone for an additional 2 months. 2) If the patient shows neither symptomatic nor radiographic improvement, prior TB is unlikely and therapy is complete after treatment including at least 2 months of RIF and pyrazinamide (PZA) has been administered. For patients whose clinical suspicion is low and who are not initially receiving treatment (top of figure), if cultures remain negative, the patient has no symptoms, and the chest radiograph (CXR) is unchanged at 2 to 3 months, the 3 treatment options are as follows: 1) INH for 9 months, 2) RIF with or without INH for 4 months, or 3) RIF and PZA for 2 months. The RIF-PZA 2-month regimen should be used only for patients who are not likely to complete a longer course of treatment and can be monitored closely. EMB indicates ethambutol; Sx, signs and symptoms.*

(From Blumberg HM, Burman WJ, Chaisson RE, Daley CL, Etkind SC, Friedman LN, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med. 2003 Feb 15;167[4]:603-62; used with permission.)

High-resolution computed tomography may show associated multifocal bronchiectasis with small (<5 mm) nodular infiltrates. Bilateral nodular or interstitial lung disease (or both), isolated disease in the right middle lobe, or lingular disease is more predominant in elderly, nonsmoking women. Hypersensitivity pneumonitis caused by exposure to *M avium* complex growing in a hot tub has been reported. *Mycobacterium avium* complex is responsible for 5% of the cases of mycobacterial lymphadenitis in adults and more than 90% of the cases in children. Lymphadenopathy is usually unilateral and nontender. Disseminated disease caused by NTM manifests as a fever of unknown origin in immunocompromised patients without AIDS.

KEY FACTS

- ✓ Chronic pulmonary disease is caused most frequently by *M avium* complex and *M kansasii*
- ✓ Pulmonary disease is more common in older adults, persons with underlying chronic obstructive pulmonary disease, smokers, persons who abuse alcohol, and some children with cystic fibrosis. More than 90% of the patients have bronchiectasis or small nodules without predilection for any lobe. High-resolution computed tomography may show associated multifocal bronchiectasis with small (<5 mm) nodular infiltrates

HIV-infected persons are at high risk for NTM infections. More than 95% of NTM disease in HIV-infected persons is caused by the *M avium* complex. In persons with AIDS, disseminated infection occurs in up to 40% and localized infection in 5%; dissemination is more likely in those with a CD4 cell count less than 50/mcL. The risk of disseminated infection is 20% per year when the CD4 cell count is less than 100/mcL. Most patients present with high fever; sweats, anemia, and increased alkaline phosphatase levels are common. Dissemination is usually documented with positive blood culture results (sensitivity, 90%).

Mycobacterium kansasii is the second most common cause of NTM pulmonary disease in the United States. Approximately 90% of patients with *M kansasii* disease have cavitary infiltrates. *Mycobacterium kansasii* infection can be clinically indistinguishable from TB; however, its symptoms may be less severe and more long-term than with TB. In HIV-negative patients, common symptoms are cough (90%), purulent sputum (85%), weight loss (55%), and dyspnea (50%). In immunocompromised patients, including those with AIDS, the lung is most commonly involved and symptoms include fever, chills, night sweats, cough, weight loss, dyspnea, and chest pain. Disseminated *M kansasii* infection occurs in 20% of HIV-positive patients who have *M kansasii* pulmonary disease.

Specific skin tests are not available for the diagnosis of NTM. Routine cultures of sputum, blood, or stool are not recommended for asymptomatic patients. All specimens positive for acid-fast bacilli must be considered to indicate *M tuberculosis* until final culture results are available. Bronchoscopy or open lung biopsy is required for diagnosis in nearly 50% of cases. *Mycobacterium avium* complex is generally treated with at least 12 months of clarithromycin, rifabutin, and ethambutol. The current recommendation for treatment of pulmonary disease caused by *M kansasii* in adults is isoniazid, rifampin, and ethambutol.

Pneumocystis jiroveci Infection

Pneumocystis jiroveci (formerly *Pneumocystis carinii*) is a fungus with trophic and cyst forms. *Pneumocystis jiroveci* infections occur in immunosuppressed persons, especially those with AIDS (CD4 cell count ≤200/mcL), receiving corticosteroids with the predisone equivalent of 20 or more mg daily for 1 month or more, and who have had organ transplant. Clinical features in patients with AIDS include the gradual onset of dyspnea, fever, tachypnea, and hypoxia. In patients without AIDS, the onset is more abrupt, and progression to respiratory failure occurs quickly. Patients typically have relatively normal findings on lung examination and a patchy or diffuse interstitial or alveolar process on chest radiography. The typical computed tomographic finding is ground-glass attenuation. Although the level of lactate dehydrogenase may be increased, routine laboratory data are often unhelpful. The diagnosis can be made with microscopic examination or polymerase chain reaction of induced sputum, bronchoalveolar lavage, or lung biopsy.

KEY FACTS

- ✓ *Pneumocystis jiroveci* infections occur in immunosuppressed persons, especially those with AIDS (CD4 cell count ≤200/mcL) and those who have had organ transplant
- ✓ Clinical features of *P jiroveci* infection in patients with AIDS include gradual onset of dyspnea, fever, tachypnea, and hypoxia. In patients without AIDS, onset is more abrupt, and progression to respiratory failure occurs quickly
- ✓ Patients typically have relatively normal findings on lung examination and a patchy or diffuse interstitial or alveolar process on chest radiography

Parasitic Diseases

Parasitic infections of the lung are less common in the United States than in many other parts of the world. Travelers to endemic regions may be at risk. Dirofilariasis is indigenous to the eastern and southeastern United States. Other parasitic infections, including helminthic infestations, also occur in the United States. The parasites most likely to cause pulmonary infections include *Paragonimus westermani* (paragonimiasis), *Echinococcus granulosus* (echinococcosis or hydatid disease), *Dirofilaria immitis* (dirofilariasis), *Schistosoma japonicum* and *Schistosoma mansoni* (schistosomiasis), and *Entamoeba histolytica* (amebiasis). Protozoal infections are more likely in persons with suppressed cellular immunity.

Dirofilariasis, caused by the heartworm that infects dogs, is transmitted to humans by mosquitoes. The disease is endemic to the Mississippi River Valley, southeastern United States, and the Gulf Coast. Characteristically, the infection manifests as a defined solitary lung nodule or multiple lung nodules that have a diameter of 1.5 to 2.5 cm. Eosinophilia occurs in less than 15% of patients. Serologic tests may aid in the diagnosis.

Echinococcosis has occurred in Alaska, the Upper Peninsula of Michigan, and the southwestern United States. When persons have echinococcosis lung disease, chest radiography shows well-defined round or oval cystic or solid lesions up to 15 cm in diameter. Cyst rupture can cause anaphylactic shock, hypersensitivity reactions, and seeding of adjacent anatomical areas. Liver involvement (which develops in 40% of lung disease cases) and positive serologic findings are common.

Paragonimiasis is more likely in immigrants from Southeast Asia, but sporadic cases occur in the United States. It is transmitted typically through consumption of raw or undercooked crabs or crayfish. Respiratory characteristics resemble those of chronic bronchitis, bronchiectasis, or tuberculosis. Profuse, brown-colored sputum and hemoptysis can be seen. Pleural effusion is relatively common; peripheral eosinophilia also is common. Ova can be found in pleural fluid, bronchial wash, or sputum.

Strongyloidiasis involving the lungs may mimic asthma with eosinophilia. Risk factors include corticosteroid use, age older than 65 years, chronic lung disease, and chronic debilitating illness. Pulmonary signs and symptoms include cough, shortness of breath, wheezing, and hemoptysis in more than 90% of patients and pulmonary infiltrates in 90%. A series of 20 patients with pulmonary strongyloidiasis showed that acute respiratory distress syndrome developed in 9 (45%). Preexisting chronic lung disease and the development of acute respiratory distress syndrome are important predictors of a poor prognosis.

49

Sexually Transmitted, Urinary Tract, and Gastrointestinal Tract Infections[a]

JENNIFER A. WHITAKER, MD, MS; M. RIZWAN SOHAIL, MD

Sexually Transmitted Infections

Sexually transmitted infections (STIs) remain a major public health burden. About 20 million STIs occur annually in the United States. The 3 nationally reported STIs in the United States are chlamydia, gonorrhea, and syphilis. Of these, chlamydia is the most commonly reported. Other common STIs that are not nationally reported include human papillomavirus (HPV) infection, herpes simplex virus (HSV) infection, and trichomoniasis. Although selected types of HPV are preventable with vaccination, other STIs require effective barriers to prevent transmission. These infections are characterized by their clinical presentations: 1) genital ulcers and lesions, 2) urethritis, 3) pelvic inflammatory disease (PID), 4) vulvovaginitis and cervicitis, and 5) urinary tract infections.

Genital Ulcers and Lesions

Chancroid

In the United States, patients who present with genital ulcers usually have genital herpes, syphilis, or, less commonly, chancroid. These conditions are associated with an increased risk of transmission and acquisition of HIV infection. The combination of a painful genital ulcer (Figure 49.1) and tender suppurative inguinal adenopathy (Figure 49.2) is highly suggestive of chancroid, which is caused by *Haemophilus ducreyi*. The prevalence of this infection has decreased over time in the United States, and chancroid is now relatively uncommon. Clinical inspection may not distinguish among genital herpes, syphilis, and chancroid, and thus all patients with genital ulcers should have syphilis serologic testing and HSV cell culture or polymerase chain reaction (PCR) test (preferred method). In areas where chancroid is prevalent, such as Africa and other tropical and subtropical regions, specialized culture for *H ducreyi* can be performed. In the United States, microbiologic diagnosis through culture and PCR may not be available. For the clinical definition of chancroid to be met, all of the following criteria must be met: 1) the patient has at least 1 painful genital ulcer, 2) the clinical presentation is typical for chancroid, 3) the patient has no evidence of syphilis on a serologic test performed 7 days or more after onset of ulcer, and 4) the result of a PCR test or culture for HSV performed on the ulcer exudate is negative.

KEY FACT

✓ In the United States, patients who present with genital ulcers usually have genital herpes, syphilis, or chancroid

Chancroid is treated with azithromycin (1 g orally once), ceftriaxone (250 mg intramuscularly once), or ciprofloxacin (500 mg orally twice daily for 3 days). A person who has had

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[a] Portions previously published in Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03):1-137.

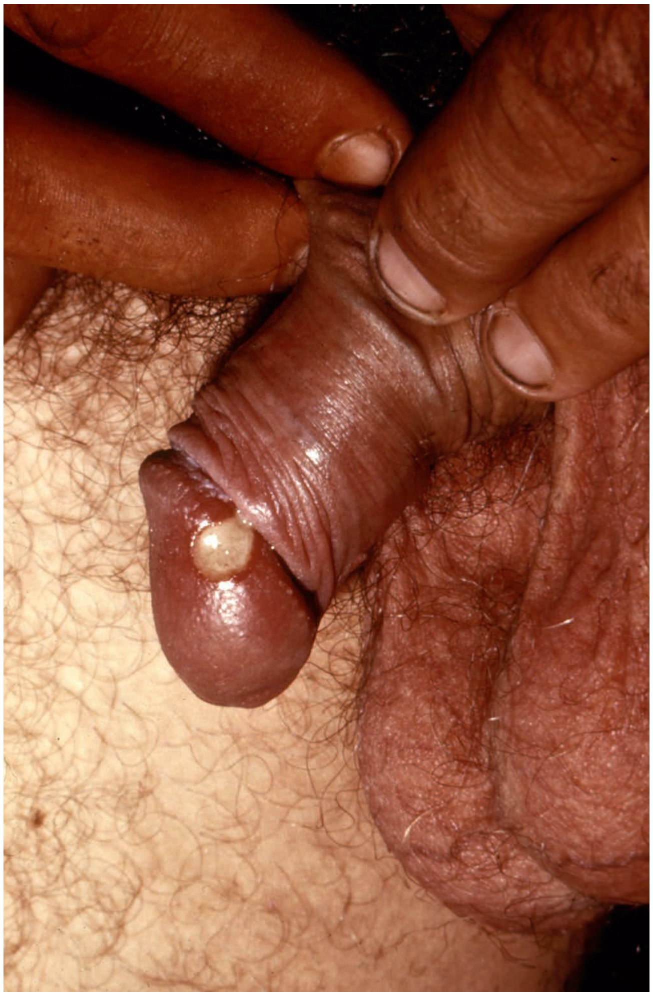

Figure 49.1. *Painful Genital Ulcer Caused by* Haemophilus ducreyi *(Chancroid).*

(From Centers for Disease Control and Prevention. Penile chancroid lesion [Internet]. Atlanta [GA]: Centers for Disease Control and Prevention; c1974 CDC/Joe Miller. Available from: http://phil.cdc.gov/ phil/ details.asp?pid=3728.)

sexual contact with an index patient during the 10 days preceding the patient's onset of symptoms should receive prophylactic treatment.

Herpes Simplex Virus

At least 50 million persons in the United States are infected with HSV type 1 or type 2. Most of them have not received a diagnosis of genital herpes. Infected persons intermittently shed virus from the genital tract despite a lack of symptoms, and this viral shedding can lead to transmission. Symptomatic infection typically presents as a few painful, clustered vesicles with an erythematous base (Figure 49.3). The preferred diagnostic tests to identify HSV in specimens from genital lesions are cell culture and PCR test (which is more sensitive than culture).

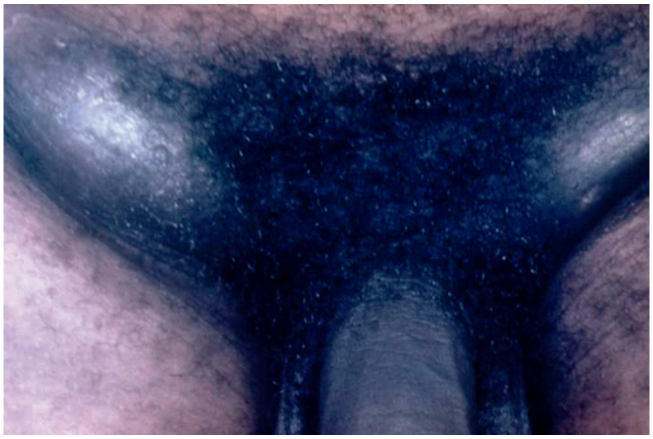

Figure 49.2. *Tender Suppurative Inguinal Adenopathy in a Patient With Chancroid.*

(From Centers for Disease Control and Prevention. Chancroid infection spread to inguinal lymph nodes [Internet]. Atlanta [GA]: Centers for Disease Control and Prevention; c1971 CDC/Susan Lindsley. Available from: http:// phil.cdc.gov/phil/details.asp?pid=5811.)

Antivirals are helpful when they are used to treat first and recurrent episodes or when used as daily suppressive therapy. Recommended regimens for a first episode of genital HSV include acyclovir (400 mg orally 3 times a day), famciclovir (250 mg orally 3 times a day), and valacyclovir (1 g orally twice a day). Treatment duration for a first episode is 7 to 10 days.

KEY FACT

✓ Antivirals are beneficial for first and recurrent episodes of HSV or when used as daily suppressive therapy

Because recurrences are common, especially with HSV type 2, episodic or continuous suppressive antiviral therapy with acyclovir (400 mg orally twice a day), famciclovir (250 mg orally twice a day), or valacyclovir (500 mg or 1g orally once a day) is equally effective for reducing the frequency of recurrences. Daily

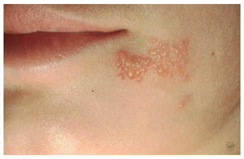

Figure 49.3. *Painful, Clustered Vesicles With an Erythematous Base Due to Herpes Simplex Virus.*

(From American Academy of Dermatology. Herpes simplex: overview [Internet]. c2018. Available from: https://www.aad.org/public/diseases/ contagious-skin-diseases/herpes-simplex; used with permission.)

treatment with valacyclovir (500 mg a day) decreases the rate of HSV type 2 transmission in discordant, heterosexual couples.

HSV in Pregnancy

In the first trimester of pregnancy, development of primary HSV infection may be associated with chorioretinitis and microcephaly in the fetus. The risk of HSV transmission to the baby from an infected mother is 30% to 50% among women who acquire genital herpes near the time of delivery, 3% for women with a recurrence at delivery, and less than 1% among women with histories of recurrent herpes but no lesions at delivery. Prevention of neonatal herpes relies on preventing acquisition of genital HSV late in pregnancy and avoiding exposure of the infant to herpetic lesions during delivery. Women without known genital herpes should be counseled to avoid intercourse during the third trimester with partners known to have genital herpes or in whom it is suspected. Pregnant women without known orolabial herpes should be advised to avoid receptive oral sex during the third trimester with partners known to have orolabial herpes or in whom it is suspected.

KEY FACT

✓ In the first trimester of pregnancy, development of a primary HSV infection may be associated with chorioretinitis and microcephaly in the fetus

At the onset of labor, all women should be questioned about symptoms of genital herpes, including prodromal symptoms, and be examined carefully for herpetic lesions. Women without symptoms or signs of genital herpes or its prodrome can deliver vaginally. Acyclovir treatment late in pregnancy reduces the frequency of cesarean sections among women who have recurrent genital herpes because it diminishes the frequency of recurrences at term. Women with recurrent genital herpetic lesions at the onset of labor should deliver by cesarean section to prevent neonatal herpes.

Syphilis

Syphilis is caused by the spirochete *Treponema pallidum*. The incidence of syphilis is highest in large, urban populations and in men who have sex with men. Called the *great masquerader*, syphilis may present with various manifestations, depending on the stage of disease, including a painless genital ulcer or chancre at the infection site; rash; mucocutaneous lesions; lymphadenopathy; cardiac, neurologic, and ophthalmic manifestations; auditory abnormalities; gummatous lesions; or simply a positive serologic test result. Because of the wide variation and transient nature of its manifestations, syphilis is often overlooked.

KEY FACT

✓ Called the *great masquerader*, syphilis may present with various manifestations, depending on disease stage, including a painless genital ulcer or chancre at the infection site; rash; mucocutaneous lesions; lymphadenopathy; cardiac, neurologic, and ophthalmic manifestations; auditory abnormalities; gummatous lesions; and positive serologic test result

Serologic tests for syphilis differ by laboratory. Some centers use the enzyme immunoassay for syphilis immunoglobulin G as a screening test, followed by the nontreponemal test of rapid plasma reagin (RPR). Other centers use the RPR test initially and confirm its result with a more specific test, such as the fluorescent treponemal antibody absorption test (Table 49.1). Results of this test are positive before VDRL testing (nontreponemal test), and thus they may be positive without a positive VDRL result in primary syphilis cases. VDRL results may be negative in 30% of patients with primary syphilis and can be negative also in late-latent infections (those that occur >1 year after secondary syphilis).

A **chancre** (clean, indurated ulcer) is the main manifestation of primary syphilis (Figure 49.4). It occurs at the site of inoculation and is painless. The incubation period is 3 to 90 days. Chancre should be distinguished from HSV (painful) and **chancroid** (painful exudative ulcer). Primary syphilis can be diagnosed with dark-field examination of a specimen taken from the genital ulcer.

Key Definitions

Chancre: *A clean, indurated ulcer and the main manifestation of primary syphilis, usually painless.*

Chancroid: *A painful exudative ulcer.*

Table 49.1 • Laboratory Diagnosis of Syphilis

	Test, % Positive		
Syphilis	**VDRL**	**FTA-ABS**	**MHA-TP**
Primary	70	85	50-60
Secondary	99	100	100
Tertiary	70	98	98

Abbreviations: FTA-ABS, fluorescent treponemal antibody absorption; MHA-TP, microhemagglutination assay for *Treponema pallidum*.

From Hook EW III. Syphilis. In: Goldman L, Schafer AI, editors. Goldman-Cecil medicine. 25th ed. Philadelphia (PA): Elsevier Saunders; c2016. p. 2013-20.e2; used with permission.

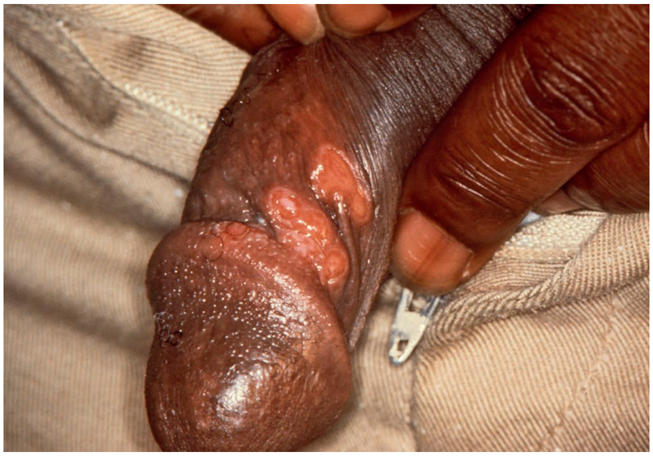

Figure 49.4. *Painless Ulcer (Chancre) Due to Primary Syphilis.* (From Centers for Disease Control and Prevention. Chancres on the penile shaft due to a primary syphilitic infection caused by Treponema pallidum bacteria [Internet]. Atlanta [GA]: Centers for Disease Control and Prevention; c1978 CDC/M. Rein. Available from: http://phil.cdc.gov/ phil/details.asp?pid=6803.)

The manifestations of secondary syphilis result from hematogenous dissemination and usually occur 2 to 8 weeks after appearance of the chancre. The chancre can occur in the vagina or rectum and not be noticed. Constitutional symptoms occur, in addition to a rash, mucocutaneous lesions (Figure 49.5), alopecia, **condylomata lata** (ie, broad and flat verrucous syphilitic lesions located in warm, moist intertriginous areas, especially about the anus and genitals [Figure 49.6]), lymphadenopathy, and various other symptoms and signs. The diagnosis is based on clinical findings and the results of serologic testing. The condition resolves spontaneously without treatment.

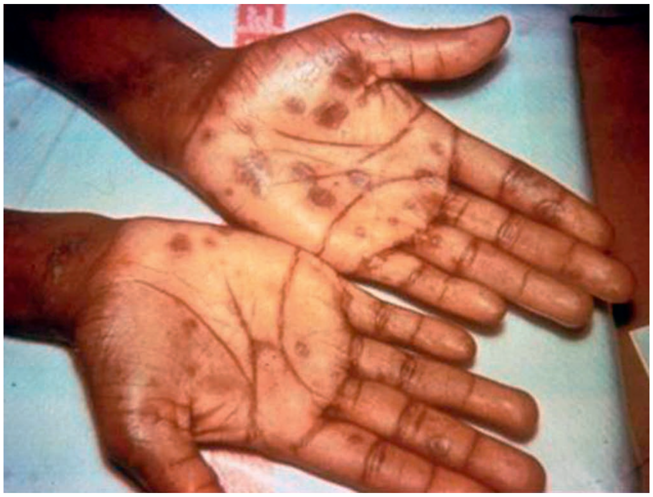

Figure 49.5. *Cutaneous Lesions in Secondary Syphilis.* (From Centers for Disease Control and Prevention. Papulosquamous syphilids, or cutaneous eruptions of syphilis [Internet]. Atlanta [GA]: Centers for Disease Control and Prevention; c1971 CDC/Susan Lindsley. Available from: http://phil.cdc.gov/phil/details.asp?pid=2369.)

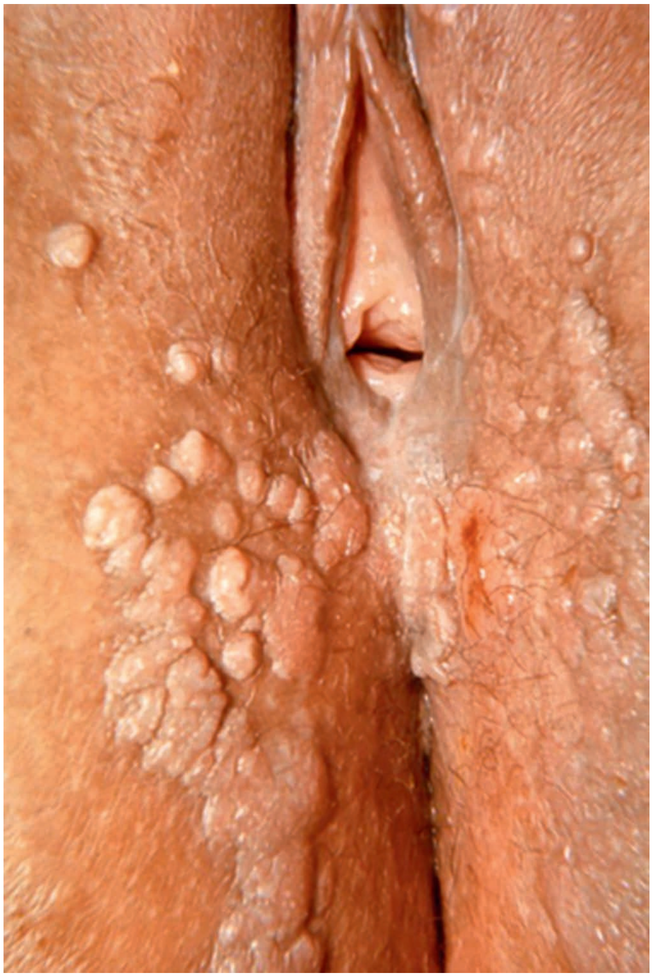

Figure 49.6. *Condylomata Lata in Secondary Syphilis.* (From Science Source. Secondary syphilitic lesions: image number BT4983 [Internet]. Science Source Images: New York [NY] [cited 2015 Nov 25]. Available from: http://images.sciencesource.com/preview/BT4983.html; used with permission.)

Key Definition

Condylomata lata: *Broad, flat verrucous syphilitic lesions occurring in warm, moist intertriginous areas, especially in the anal and genital areas.*

Latent syphilis is the asymptomatic stage after symptoms of secondary syphilis subside. Cases of secondary syphilis that occur after 1 year are classified as late latent. The diagnosis is based on the results of serologic testing. For latent syphilis, examination of cerebrospinal fluid (CSF) is indicated before treatment in patients with neurologic (cranial nerve dysfunction, auditory abnormalities, meningitis, stroke, acute or chronic altered mental status, and loss of vibration sense) or ophthalmic abnormalities (uveitis, iritis, retinitis, and Argyll Robertson pupils [accommodation reflex present and light reflex absent]), before treatment in patients with other evidence of active tertiary syphilis (eg, aortitis, gummas), and before re-treatment of relapses. Patients with ocular complaints or abnormalities should undergo a formal ophthalmologic examination. All persons living with HIV who have a positive test for syphilis should have a careful neurologic examination. Prior STI guidelines had advocated for CSF examination in persons living with HIV who had an RPR titer more than 1:32, but the updated guidelines recommend CSF analysis only in cases of neurologic or ocular symptoms or abnormalities.

Tertiary syphilis can involve any body system (eg, cardiovascular aortitis involving the ascending aorta, which can cause aneurysms and aortic regurgitation; gummatous osteomyelitis; hepatitis). However, neurosyphilis is the most common manifestation of tertiary syphilis in the United States. Neurosyphilis is often asymptomatic. Symptomatic disease is divided into several clinical syndromes that may overlap and occur at any time after primary infection. CSF abnormalities in neurosyphilis may include mononuclear pleocytosis and an increased protein value. CSF VDRL testing is only 30% to 70% sensitive. By comparison, the CSF fluorescent treponemal antibody absorption test is highly sensitive (>90% sensitivity). Any CSF abnormality in a patient who is seropositive for syphilis must be investigated. The spectrum of neurosyphilis includes meningovascular syphilis (occurs 4-7 years after infection and presents with stroke or cranial nerve abnormalities) and parenchymatous syphilis (occurs decades after infection and may present as general paresis or chronic progressive dementia or as tabes dorsalis resulting in sensory ataxia, lightning pains, autonomic dysfunction, and optic atrophy).

KEY FACT

✓ Neurosyphilis is the most common manifestation of tertiary syphilis in the United States

Treatment of syphilis is summarized in Table 49.2. After treatment (especially in early syphilis), 10% to 25% of patients may experience a Jarisch-Herxheimer reaction, manifested by varying degrees of fever, chills, myalgias, headache, tachycardia, and hypotension. This reaction lasts 12 to 24 hours and can be managed symptomatically.

Pregnant patients should receive a penicillin-based regimen for treatment of all stages of syphilis. If a pregnant patient has a penicillin allergy, she should receive therapy for desensitization to penicillin.

HIV testing should be performed in all patients with syphilis. For early and secondary syphilis, follow-up clinical and serologic testing (ie, RPR) should be performed at 6 and 12 months. Re-treatment with 3 weekly injections of 2.4 million U of benzathine penicillin G should be given to patients with signs or symptoms that persist or whose RPR result shows a sustained 4-fold increase in titer. It is important to take a detailed sexual history to determine whether a patient was exposed to syphilis since the time of treatment. It is also important to ensure that a patient's sexual partners were treated for syphilis. If the RPR titer does not decrease 4-fold within 6 months, consideration also should be given to re-treatment.

Table 49.2 • Treatment of Syphilis

Condition	**Recommended Regimen**	**Alternative Regimen**
Early syphilis (primary, secondary, or early latent [<1 y])	Benzathine penicillin G (2.4 million U given IM once)	Doxycycline (100 mg twice daily for 14 d) *Or* Tetracycline (500 mg orally 4 times daily for 14 d) *Or* Erythromycin (500 mg orally 4 times daily) (least-effective treatment)
Late syphilis (cardiovascular disease, gumma, or late latent [≥1 y])	Benzathine penicillin (2.4 million U given IM weekly for 3 wk)	Doxycycline (100 mg orally twice daily for 4 wk) *Or* Tetracycline (500 mg orally 4 times daily)
Neurosyphilis	Aqueous penicillin G (12 million-24 million U given IV daily for 10 to 14 d)	Procaine penicillin (2.4 million U given IM daily) *plus* probenecid (500 mg 4 times daily) for 10 to 14 d

Abbreviations: IM, intramuscularly; IV, intravenously.

Patients with latent syphilis should have follow-up testing at 6, 12, and 24 months. If the RPR result increases 4-fold, if a high titer (>1:32) fails to decrease 4-fold within 12 to 24 months, or if signs or symptoms attributable to syphilis occur, a CSF examination should be repeated to rule out neurosyphilis, and re-treatment should be done accordingly.

Follow-up in patients who receive therapy for neurosyphilis should include testing of CSF every 6 months if CSF pleocytosis was present initially; this testing is done until the results are normal. If the cell count is not decreased at 6 months or the CSF is not entirely normal at 2 years, re-treatment should be considered.

Urethritis Syndromes

The clinical syndrome of urethral pain and discharge is often associated with gonorrhea, chlamydia, and other causes of nongonococcal urethritis (NGU). Urethritis is diagnosed on the basis of the following findings: mucopurulent or purulent discharge, a Gram stain of urethral secretions with 5 or more leukocytes per oil-immersion field, or a positive result of leukocyte

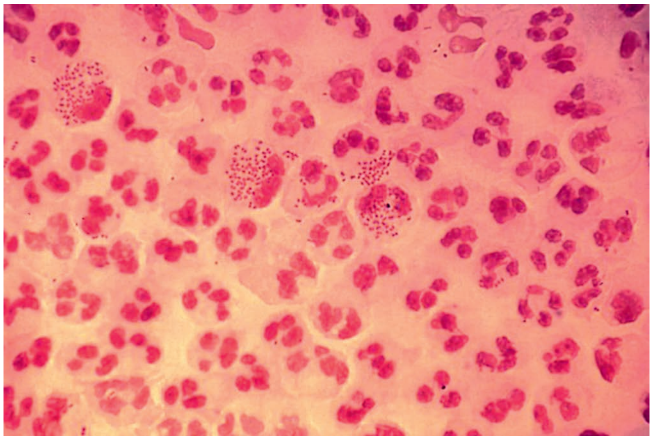

Figure 49.7. *Gram-Negative Intracellular Diplococci in Gonococcal Urethritis (Gram Stain).*

(From Centers for Disease Control and Prevention. Histopathology in an acute case of gonococcal urethritis using Gram-stain technique [Internet]. Atlanta [GA]: Centers for Disease Control and Prevention. Available from: http://phil.cdc.gov/phil/ details.asp?pid=4085.)

esterase test on first-void urine. The presence of gram-negative intracellular diplococci on a urethral smear (Figure 49.7) is indicative of gonorrhea infection and is often accompanied by chlamydial infection. NGU is diagnosed when microscopy indicates inflammation without gram-negative intracellular diplococci. Urine or urethral exudates should be tested for gonorrhea and *Chlamydia trachomatis*. A frequent cause of NGU (15%-55% of cases), *C trachomatis* nevertheless varies in prevalence by age-group, with lower prevalence among older men. *Mycoplasma genitalium* is emerging as an increasingly recognized cause of NGU. *Trichomonas vaginalis* may also cause NGU in men who have sex with women. Complications of NGU among men infected with *C trachomatis* include epididymitis, prostatitis, and reactive arthritis syndrome. Treatment should be initiated at diagnosis of NGU with azithromycin 1 g orally for one dose or doxycycline 100 mg orally twice daily for 7 days.

KEY FACT

✓ Urethritis diagnosis is based on finding mucopurulent or purulent discharge, Gram stain of urethral secretions with 5 leukocytes or more per oil-immersion field, or positive result of leukocyte esterase test on first-void urine

Gonorrhea

Neisseria gonorrhoeae is a gram-negative intracellular diplococcus. Although rates of gonorrhea have remained stable in the United States, resistance to antimicrobials has increased. The infection often causes symptomatic urethritis and discharge in men, but it has few symptoms in women and may lead to cervicitis, infertility, ectopic pregnancy, and chronic pelvic pain. Gonococcal proctitis may occur in both men and women who have anal-receptive intercourse. Annual screening for *N gonorrhoeae* infection is recommended for all sexually active women younger than 25 years and in older women with risk factors for STIs. Gonococcal pharyngitis is often asymptomatic. Gonococcal pharyngitis or proctitis may be diagnosed by sending specimens for gonococcal culture. Gonorrhea can be diagnosed in men from Gram stain of urethral exudate showing intracellular gram-negative diplococci (Figure 49.7). A nucleic acid amplification test (NAAT) of a urine or urethral-cervix base can also be used for diagnosis. NAAT tests for gonorrhea or chlamydia have not been cleared by the US Food and Drug Administration for testing of oropharyngeal or rectal sites. However, some laboratories have developed NAAT tests approved by Clinical Laboratory Improvement Amendments, and these are commercially available. NAAT testing is more sensitive than culture.

KEY FACT

✓ Although gonorrhea rates have stayed stable in the United States, antimicrobial resistance in gonorrhea has increased

Resistance to penicillin, tetracycline, and, most recently, fluoroquinolones and cephalosporins has limited the gonorrhea treatment options. The recommended treatment for gonorrhea has changed over time because of the emergence of antibiotic resistance. The recommended treatment of gonorrhea in the United States consists of only 1 regimen: ceftriaxone (250 mg intramuscularly) plus azithromycin (a single 1-g dose). These 2 medications should be preferentially administered together and the patient observed. Oral cefixime (400 mg once daily) is no longer recommended as a first-line oral option. Alternative therapies are limited for patients who are allergic to β-lactam. Spectinomycin is not available in the United States. Limited data suggest that high-dose azithromycin (2 g in 1 dose) therapy might be an option, although this regimen should generally be avoided as solitary treatment of gonorrhea because of concern about drug resistance. Follow-up NAAT at 3 weeks after treatment is recommended for all pregnant women. All patients with a sexually transmitted disease should be tested for HIV infection. Sexual partners should be offered evaluation and treatment.

In 1% to 3% of patients with *N gonorrhoeae*, the infection may lead to disseminated gonococcal infection. Risk factors include complement deficiency, pharyngeal infection, pregnancy, and menstruation. The disseminated infection occurs most often in women during menstruation, when sloughing of endometrium allows access to a blood supply, enhanced growth of gonococci due to necrotic tissue, and change in pH. Two distinct phases occur in *N gonorrhoeae* infection. The bacteremic phase may manifest as tenosynovitis (around the wrists or ankles [also called *lover's heels*]); painful, distally distributed skin lesions (macular or pustular with a hemorrhagic component); and polyarthralgias involving knees and elbows (the classic dermatitis arthritis syndrome). Results of synovial fluid testing are frequently negative. The nonbacteremic phase follows 1 week later and may present as monoarticular infectious arthritis of the knee, wrist, and ankle; results of joint culture are positive in about 50% of cases. Culture and NAAT specimens should be obtained from the appropriate genital and extragenital sites depending on sexual activity.

KEY FACT

✓ Risk factors for disseminated *N gonorrhoeae* infection include complement deficiency, pharyngeal infection, pregnancy, and menstruation

Treatment of disseminated gonococcal infection should be done in conjunction with an infectious diseases specialist. All positive cultures should be sent for antimicrobial susceptibility testing.

Diseases Characterized by NGU and Cervicitis

Chlamydia trachomatis genital infection is the most common reportable STI. This organism causes urethritis in men and mucopurulent cervicitis, endometritis, and PID in women. Its sequelae include tubal infertility, chronic pelvic pain, and ectopic pregnancy. Because this infection may be asymptomatic in one-half of affected men and three-fourths of affected women, screening for *C trachomatis* is recommended for all sexually active women age 24 years or younger and older women who have risk factors for infection.

KEY FACT

✓ *Chlamydia trachomatis* genital infection is the most common reportable STI

The diagnosis is most often made from NAATs or from urine or urethrocervical specimens. Treatment of infected persons, whether or not the infection is symptomatic, reduces *C trachomatis* transmission. Two regimens are highly effective, and the treatment choice depends on patient compliance. Doxycycline (100 mg twice daily for 7 days) or azithromycin (a single 1-g oral dose) is standard treatment. Infected persons should abstain from sexual activity until 1 week after treatment is completed. Women with *C trachomatis* cervicitis should be rescreened with NAAT at 3 to 4 months posttreatment. *Ureaplasma urealyticum, T vaginalis, M genitalium*, and HSV are less common causes of nongonococcal urethritis. If urethritis fails to resolve and reinfection or relapse of a chlamydial infection has been excluded, *Trichomonas* or tetracycline-resistant *Ureaplasma* infection should be considered. In this situation, empirical treatment consists of metronidazole (2 g orally in a single dose) plus an erythromycin-base treatment (500 mg orally 4 times daily for 7 days).

Epididymitis

This condition usually presents as a unilateral, painful scrotal swelling. In men who are sexually active and young (age <35 years), *C trachomatis* and *N gonorrhoeae* are the common pathogens of epididymitis. Sexually transmitted acute epididymitis is usually accompanied by asymptomatic urethritis and absence of bacteruria. In contrast, aerobic gram-negative rods and enterococci predominate in older men with epididymitis, which is frequently associated with urinary tract abnormalities or instrumentation. Although epididymitis is primarily a clinical diagnosis, ultrasonography has a sensitivity of 70% and a specificity of 88% for diagnosing acute epididymitis. The diagnostic evaluation of men in whom epididymitis is suspected should include a Gram stain of urethral secretions, a leukocyte esterase test of first-void urine, and microscopic examination of first-void urine sediment (positive result, ≥10 leukocytes per high-power field).

Empirical treatment includes ceftriaxone (250 mg intramuscularly) plus doxycycline (100 mg orally twice daily for 10 days). In older men with test results that are negative for gonorrhea and *Chlamydia*, the treatment advised is empirical therapy with oral levofloxacin (500 mg daily for 10 days) or treatment based on culture results (if positive).

Pelvic Inflammatory Disease

In reproductive-age women, PID is associated with considerable long-term sequelae, such as infertility, ectopic pregnancy, tubo-ovarian abscess, and chronic pelvic pain. The organisms responsible include *N gonorrhoeae, C trachomatis, Mycoplasma hominis*, and various aerobic gram-negative rods and anaerobes. Fitz-Hugh-Curtis syndrome is an acute perihepatitis caused by direct extension of *N gonorrhoeae* or *C trachomatis* infection to the liver capsule. *Actinomyces* species can be a pathogen in patients with an intrauterine device. Diagnosis of PID is based on clinical findings, including lower abdominal or adnexal tenderness, cervical motion tenderness, fever, abnormal cervical discharge, and evidence of *N gonorrhoeae* or *C trachomatis* infection. Early empirical therapy is recommended for women at risk. Sonography and laparoscopy are reserved for complicated cases.

KEY FACT

✓ PID in reproductive-age women is associated with such long-term sequelae as infertility, ectopic pregnancy, tubo-ovarian abscess, and chronic pelvic pain

The goal of treatment is to prevent complications. Most women can receive treatment as outpatients and be reassessed within 1 to 3 days. Hospitalization is indicated when the outpatient therapy is precluded by severe nausea and vomiting, the diagnosis is uncertain, pelvic abscess or peritonitis is present, the patient is pregnant or an adolescent, or noncompliance is suspected. Table 49.3 outlines the treatment of PID.

Tubo-ovarian abscess may be characterized by an adnexal mass on physical examination or radiographic examination or by failure of antimicrobial therapy. Most abscesses less than 5 cm in diameter respond to medical therapy alone with the preferred regimen of ampicillin, gentamicin, and clindamycin. Large abscesses (>10 cm) often necessitate operation.

Table 49.3 • Treatment Regimens for Pelvic Inflammatory Diseases

Infection	**Recommended Regimen**	**Alternative Regimen**
Pelvic inflammatory disease[a]	Parenteral A Cefotetan (2 g IV every 12 h) *Or* Cefoxitin (2 g IV every 6 h) *Plus* Doxycycline (100 mg orally or IV every 12 h)	Parenteral Ampicillin-sulbactam (3 g IV every 6 h) *Plus* Doxycycline (100 mg orally or IV every 12 h)
	Parenteral B Clindamycin (900 mg IV every 8 h) *Plus* Gentamicin[b]	
	Oral[c] Ceftriaxone (250 mg IM in single dose) *Plus* Doxycycline (100 mg orally twice daily for 14 d) *with or without* metronidazole (500 mg orally twice daily for 14 d)	Fluoroquinolones[d] Levofloxacin (500 mg orally once daily) or oxacin (400 mg twice daily for 14 d) *with or without* metronidazole (500 mg orally twice daily for 14 d)
	Or Cefoxitin (2 g IM in single dose) and probenecid (1 g orally concurrently in single dose) *Plus* Doxycycline (100 mg orally twice daily for 14 d) *with or without* metronidazole (500 mg orally twice daily for 14 d)	
	Or Other parenteral third-generation cephalosporin[e] *Plus* Doxycycline 100 mg orally twice daily for 14 d *with or without* metronidazole 500 mg orally twice daily for 14 d	
Epididymitis	Ceftriaxone 250 mg IM in a single dose *Plus* Doxycycline 100 mg orally twice daily for 10 d	
	Ofloxacin[f] 300 mg orally twice daily for 10 d *Or* Levofloxacin 500 mg orally once daily for 10 d	

Abbreviations: IM, intramuscularly; IV, intravenously.

[a] Parenteral and oral therapies seem to have similar clinical efficacy for women with pelvic inflammatory disease of mild or moderate severity. Clinical experience should guide decisions regarding transition to oral therapy, which usually can be initiated within 24 hours of clinical improvement.

[b] Loading dose (2 mg/kg) IV or IM, followed by maintenance dose (1.5 mg/kg) every 8 hours. Single daily dosing may be substituted.

[c] Oral therapy can be considered for women with mild to moderately severe acute pelvic inflammatory disease because the clinical outcomes with oral therapy are similar to those with parenteral therapy. Women whose disease does not respond to oral therapy within 72 hours should be reevaluated to confirm the diagnosis and should be administered parenteral therapy on either an outpatient or an inpatient basis.

[d] If parenteral cephalosporin therapy is not feasible, use of fluoroquinolones with or without metronidazole may be considered when the community prevalence and individual risk of gonorrhea are low. Tests for gonorrhea must be performed before initiating therapy.

[e] Ceftizoxime or cefotaxime.

[f] For acute epididymitis most likely caused by enteric organisms or with negative gonococcal culture or nucleic acid amplification test.

Data from Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03):1-137.

Modified from Walker CK, Wiesenfeld HC. Antibiotic therapy for acute pelvic inflammatory disease: the 2006 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines. Clin Infect Dis. 2007 Apr 1;44 Suppl 3:S111-22; used with permission.

Vaginitis

Vaginitis is characterized by vaginal discharge or vulvar itching, odor, or irritation. The 3 entities most frequently associated with vaginal discharge are bacterial vaginosis, trichomoniasis, and vulvovaginal candidiasis.

Bacterial Vaginosis

Bacterial vaginosis is the most common vaginal infection affecting women of childbearing age. It occurs because of a change in local vaginal ecologic characteristics from a flora of predominant lactobacilli to one of various anaerobic bacteria. Organisms associated with the syndrome include *Atopobium vaginae, Gardnerella* species, *Prevotella* species, *Mobiluncus* species, and *M hominis*. Risk factors for bacterial vaginosis include new or multiple sex partners, excessive douching, and a lack of vaginal lactobacilli. Bacterial vaginosis has been associated with increased risk for STIs and low-birth-weight infants.

KEY FACT

✓ Risk factors for bacterial vaginosis include new or multiple sex partners, douching, and a lack of vaginal lactobacilli

Bacterial vaginosis can be diagnosed with clinical or microbiologic criteria. Clinical criteria require 3 of the following: grayish white discharge that is homogeneous and coats the vaginal walls; bacteria obscuring the borders of vaginal epithelial cells, giving them a stippled appearance (so-called clue cells) on wet-mount examination (Figure 49.8); a vaginal fluid pH more than 4.5; and a fishy smell when secretion is mixed with 10% potassium hydroxide (a positive "whiff" test). Microbiologic criteria require microscopic examination with Gram stain that shows predominantly *Gardnerella* or *Mobiluncus* morphotype, or both, with few or absent lactobacilli. Rapid nucleic acid test using DNA probe–based assessment for high concentrations of *Gardnerella vaginalis* may also be used. Culture for *G vaginalis* is not recommended because this organism is frequently present in women without bacterial vaginosis.

KEY FACT

✓ Clinical criteria for bacterial vaginosis require 3 of the following: grayish white, homogeneous discharge that coats the vaginal walls, clue cells (bacteria obscuring the borders of vaginal epithelial cells, giving a stippled appearance) on wet-mount examination, vaginal fluid pH greater than 4.5, and a fishy smell when secretion is mixed with 10% potassium hydroxide

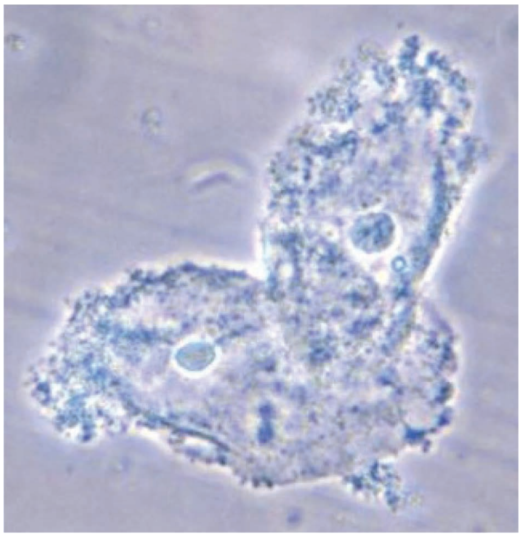

Figure 49.8. Clue Cells With Bacteria Obscuring the Borders of Vaginal Epithelial Cells in a Patient With Bacterial Vaginosis. (From Centers for Disease Control and Prevention. Bacteria adhering to vaginal epithelial cells [Internet]. Atlanta [GA]: Centers for Disease Control and Prevention; c1978 CDC/M. Rein. Available from: http://phil.cdc.gov/phil/details.asp?pid=3720.)

Recommended treatment regimens include metronidazole (500 mg orally twice daily for 7 days), topical clindamycin cream (2% for 7 days), or metronidazole gel (0.75% intravaginal applicator nightly for 5 days). Topical clindamycin cream appears less efficacious than metronidazole. Clindamycin (300 mg orally twice daily for 7 days) is an alternative treatment that may be used if the first-line recommended regimens cannot be used. Single-dose metronidazole therapy should not be used. Recurrence of bacterial vaginosis is common. Treatment of recurrent disease should include re-treatment followed by a prolonged course of twice-weekly metronidazole gel.

Bacterial vaginosis has been associated with adverse pregnancy outcomes. All symptomatic pregnant women should receive treatment.

Trichomoniasis

Trichomonas vaginitis (trichomoniasis) presents as malodorous yellow-green vaginal discharge with vulvar irritation, dysuria, or dyspareunia. Petechial lesions may be noted on the cervix (called *strawberry cervix*) with colposcopy. The diagnosis is established from wet-mount examination of vaginal secretions showing the motile organisms. The vaginal pH is usually greater than 4.5. New rapid tests for *Trichomonas* in women include the 10-minute dipstick assay and the 45-minute nucleic acid probe test. Both these tests are performed on vaginal secretions and have a sensitivity greater than 83% and a specificity greater than 97%. These rapid tests are much more sensitive than the direct wet-mount examination.

KEY FACT

✓ *Trichomonas* vaginitis presents as malodorous yellow-green vaginal discharge with vulvar irritation, dysuria, or dyspareunia. Petechial lesions may be seen on the cervix at colposcopy

Treatment is with a single 2-g dose of metronidazole or tinidazole. A 7-day course of metronidazole (500 mg twice daily) is an alternative regimen. Gastrointestinal tolerance may be better with tinidazole. All partners should be examined and treated. Symptomatic pregnant women should receive a single 2-g dose of metronidazole. Because of the high rate of reinfection among women treated for trichomoniasis, *T vaginalis* repeat testing is recommended for all sexually active women within 3 months after treatment.

Vulvovaginal Candidiasis

Vulvovaginal candidiasis is the second most common cause of vaginitis. The majority of cases are due to *Candida albicans*; a smaller number are due to *Candida glabrata*. The predominant symptoms of this condition are itching, soreness, burning, and dyspareunia although not discharge. Usually there is no odor, and the discharge is scant, watery, and white. A so-called cottage cheese curd material may adhere to the vaginal wall. Microscopy with 10% potassium hydroxide added to the discharge may show characteristic pseudohyphae; however, it is insensitive for diagnosis, and culture may be needed. Complicated cases include recurrent episodes (>4 per year), have severe symptoms, involve non-*albicans Candida*, or occur in the clinical setting of immunosuppression, diabetes mellitus, or pregnancy. In severe or recurrent cases, patients should be tested for HIV infection. For uncomplicated vulvovaginal candidiasis, any of a number of topical antifungal azole agents may be used for 1 to 7 days, or a single 150-mg oral dose of fluconazole may be used. Multiple-dose oral azole therapy is reserved for severe, refractory cases. In recurrent vulvovaginal candidiasis due to *C albicans*, treatment with fluconazole (150 mg every 3 days for 3 doses, followed by 150 mg once weekly) may be effective.

KEY FACT

✓ The predominant symptoms of vulvovaginal candidiasis are itching, soreness, burning, and dyspareunia but not discharge. Usually, no odor is present, and discharge is scant, watery, and white. Whitish material that resembles cottage cheese curds may adhere to the vaginal wall

Human Papillomavirus

More than 40 types of HPV can infect the genital area. HPV types 16 and 18 cause 70% of cervical cancers, and types 31, 33, 45, 52, and 58 cause another 20% of cervical cancers. HPV types 16 and 18 also cause nearly 90% of anal cancers and a considerable proportion of oropharyngeal, vulvar, vaginal, and penile cancers. HPV types 6 and 11 cause most genital warts. The HPV vaccine currently available in the United States is a 9-valent vaccine that contains HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

The Advisory Committee on Immunization Practices recommends routine HPV vaccination for all girls at age 11 to 12 years, and vaccination may begin as early as 9 years of age. Catch-up vaccination is recommended for females 13 to 26 years old who have not completed the vaccine series. The Committee recommends HPV vaccination for males in the same age range as females. Catch-up vaccination is recommended for males 13 to 21 years old who have not completed the vaccine series. Catch-up vaccination is recommended for males up to 26 years old who have sex with other men or who have HIV infection. The Committee gives “permissive use” to perform catch-up vaccination on other men 22 to 26 years old. HPV vaccine is recommended for persons who have had prior HPV infection if they are in the recommended age range for vaccination because the vaccine can protect against HPV strains that have not yet been acquired.

Anogenital warts may be asymptomatic or may cause pain or pruritus. Anogenital warts are usually diagnosed by visual examination. If the diagnosis is uncertain or if the lesion has atypical features such as pigmentation, induration, bleeding, or ulceration, biopsy should be performed to evaluate for malignancy. Biopsy is also indicated in immunocompromised patients, such as those with HIV. Some warts may spontaneously resolve within 1 year. Others may require removal if they are symptomatic or cause psychological distress. Treatment regimens for removal depend on multiple factors: location, size, number, site, cost, convenience, and patient and clinician preferences. Clinician-administered treatment options include cryotherapy, surgical excision, or trichloroacetic acid application. Topical treatments for external anogenital warts include patient-applied imiquimod, podofilox, or sincatechins. Treatment for internal anogenital warts usually involves cryotherapy or surgical management.

Urinary Tract Infections

In Women

Urinary tract infections (UTIs) are common in women. Urinalysis should be done with or without evaluation with a Gram stain. In the absence of pyuria, a diagnosis other than UTI should be strongly considered. If pyuria and uncomplicated UTI are present, short-course treatment (3 days) may be initiated with no further testing. However, because of increasing antibiotic resistance, culturing of urine before treatment may be reasonable in some circumstances. Urine should be cultured when symptoms are not clearly suggestive of UTI, if symptoms persist or recur, if a patient recently had antibiotic therapy, if a patient has a history of infection with organisms that have antimicrobial resistance, if pyelonephritis is suspected, or if a patient has a complicated UTI. A complicated UTI includes infection associated with a condition (functional or anatomical abnormality of genitourinary tract or other disease process) that increases the risks of acquiring infection or failing therapy. The conditions associated with complicated UTI include presence of urinary catheter or stent, obstructive uropathy, modification to the urinary system (such as ileal conduit), vesiculoureteral reflux or functional abnormality, pregnancy, poorly controlled diabetes mellitus, acute or chronic kidney disease, immunosuppression, and transplantation. Common causative organisms include *Escherichia coli, Staphylococcus saprophyticus, Proteus mirabilis*, and *Klebsiella pneumoniae*.

KEY FACT

✓ In women, when pyuria and uncomplicated UTI are present, short-course treatment (3 days) should be initiated with no further testing

Staphylococcus saprophyticus is a distinct species of coagulase-negative staphylococcus that is a common cause of UTIs in young, sexually active women. Coagulase-negative staphylococci are usually resistant to the β-lactam antibiotics. However, *S saprophyticus* and *Staphylococcus lugdunensis* (another cause of UTI) are exceptions because they usually are susceptible to the penicillins, trimethoprim-sulfamethoxazole, and many other antibiotics.

KEY FACT

✓ *Staphylococcus saprophyticus* is a distinct coagulase-negative staphylococcus species that commonly causes UTIs in young, sexually active women

For the first episode of cystitis or urethritis, treatment is given but no investigation is needed. Short-course (3 days) treatment has fewer adverse effects than standard (7-10 days) therapy, and risk of infection relapse is the same. Trimethoprim-sulfamethoxazole (in areas with low levels of resistant *E coli*), nitrofurantoin, and fosfomycin are considered first-line antimicrobial options for uncomplicated UTIs. In patients whose condition does not improve in 48 hours of treatment with first-line therapy, drug resistance should be suspected and an oral fluoroquinolone should be considered. Rates of trimethoprim-sulfamethoxazole resistance among *E coli* approach 20% in some populations. If recurrence develops after 3-day therapy, subclinical pyelonephritis or drug resistance should be considered. Urologic evaluation is usually not necessary. It should be performed, however, for patients with multiple relapses, painless hematuria, a history of childhood UTI, urolithiasis, and recurrent pyelonephritis.

Asymptomatic bacteriuria ($>10^5$ colony-forming units/mL) in a midstream urine specimen should be treated only in pregnant women and in patients undergoing urinary tract instrumentation. For acute uncomplicated pyelonephritis, levofloxacin (750 mg once daily for 5 days) is equal in efficacy to 10 days of twice-daily therapy with ciprofloxacin. In patients who are sufficiently ill to require hospitalization, a third-generation cephalosporin or a fluoroquinolone can be used as empirical therapy over 10 to 14 days. If enterococci are suspected on the basis of the gram-stain evaluation, ampicillin or piperacillin should be used. Cephalosporins and trimethoprim-sulfamethoxazole should not be used to treat enterococcal UTI. Oral regimens can be substituted quickly as the patient improves. A repeat urine culture (test of cure) is recommended 1 to 2 weeks after completion of therapy only in pregnant women, children, and patients with recurrent pyelonephritis for whom suppressive therapy is being considered.

KEY FACT

✓ Asymptomatic bacteriuria ($>10^5$ colony-forming units/mL) in a midstream urine specimen should be treated only in pregnant women and patients having urinary tract instrumentation

Recurrent UTIs may occur in women even without an anatomical abnormality. Prophylaxis may be offered to women who have 2 or more symptomatic UTIs within 6 months or 3 or more over 12 months. For these patients, 3 options have been shown to be effective: continuous prophylaxis, postcoital prophylaxis, and intermittent self-treatment, depending on clinical circumstances. For postmenopausal women, vaginal estrogen supplementation is beneficial.

In Men

UTI is less common in men, but its frequency increases with age. Urologic abnormalities (such as benign prostatic enlargement) are common in older men with UTIs. Men with symptomatic dysuria should be evaluated for sexually transmitted diseases and prostatism. When a UTI is suspected, urine culture and sensitivity testing should be done. Causative organisms include *E coli* in 50% of cases, other gram-negative organisms in 25%, enterococci in 20%, and other organisms in 5%. If signs and symptoms of epididymitis, acute prostatitis, and pyelonephritis are present, these conditions should be treated accordingly. All UTIs in men are treated as complicated conditions (10-14 days of antimicrobial therapy even for cystitis). If symptoms persist or relapse, urine culture should be repeated. If results are positive again and no abnormalities are noted on imaging, a 6-week treatment may be considered for presumed prostatitis. If culture results are negative, consider further evaluation for one of the chronic prostatitis–chronic pelvic pain syndromes.

KEY FACT

✓ Men with symptomatic dysuria should receive evaluation for sexually transmitted diseases and prostatism

Gastrointestinal Infections

Toxigenic and Invasive Bacterial Diarrhea

The principal causes of toxigenic diarrhea are listed in Table 49.4, and those of invasive diarrhea are listed in Table 49.5. Fecal leukocytes are usually absent in toxigenic diarrhea. In invasive diarrhea, fecal leukocytes may be present. The travel and exposure history is critical for appropriate work-up.

Campylobacter jejuni

Campylobacter jejuni is the most common cause of sporadic acute bacterial diarrhea. Outbreaks, although infrequent, are associated with consumption of unpasteurized dairy products and undercooked poultry. The incidence of disease peaks in summer and early fall. Diarrhea may be bloody, and fever is usually present. The diagnosis is established by isolation of the organism from stool culture or PCR. Treatment is usually symptomatic because the disease tends to be self-limited. Fluoroquinolone resistance is common, especially in Asia. Erythromycin (500 mg twice daily for 5 days) or azithromycin can be used when symptoms are prolonged and severe or the host is immunocompromised.

KEY FACT

✓ *Campylobacter jejuni* is the most common cause of sporadic acute bacterial diarrhea. Outbreaks, although less common, are associated with consumption of unpasteurized dairy products and undercooked poultry

Staphylococcal Enterotoxin

Preformed enterotoxins produced by *Staphylococcus aureus* are a common cause of food poisoning in the United States. The toxins are heat stable and therefore are not destroyed by cooking the contaminated foods. Preformed toxin of *S aureus* is ingested in contaminated food. It has a short incubation period of 4 to 6 hours. Onset is abrupt, with severe vomiting (often predominates), diarrhea, and abdominal cramps. The duration of infection is 8 to 24 hours. Diagnosis is based on rapid onset, absence of fever, and history. Treatment is supportive.

Clostridium perfringens

Bacterial diarrhea caused by *Clostridium perfringens* is associated with ingestion of bacteria that produce toxin in vivo, often in improperly prepared or stored precooked foods (meat and poultry products). Food is precooked and toxin is destroyed, but spores survive; when food is rewarmed, spores germinate. When the contaminated food is ingested, toxin is produced. Diarrhea is more severe than vomiting, and abdominal cramping is prominent. Onset of symptoms is later than with *S aureus* infection. Duration of illness is 24 hours. The diagnosis is based on the later onset of symptoms, a typical history. Treatment is supportive.

Bacillus cereus Toxin

Two types of food poisoning are associated with *B cereus* infection. Profuse vomiting follows a short incubation period (1-6 hours); this is associated with the ingestion of a preformed toxin (usually in fried rice). A disease with a longer incubation occurs 8 to 16 hours after consumption; profound diarrhea develops and usually is associated with eating meat or vegetables.

Table 49.4 • Causes of Toxigenic Bacterial Diarrhea

Organism	Onset After Ingestion, h	Preformed Toxin	Fever Present	Vomiting Predominates
Staphylococcus aureus	2-6	Yes	No	Yes
Clostridium perfringens	8-16	No	No	No
Escherichia coli	12	No	No	No
Vibrio cholerae	12	No	Yes, due to dehydration	No
Bacillus cereus				
a	1-6	Yes	No	Yes
b	8-16	No	No	No
Clostridium difficile	days (variable)	No	Sometimes	No

Table 49.5 • Causes of Invasive Bacterial Diarrhea

Organism[a]	**Bloody Diarrhea Present**	**Antibiotics Effective**
Shigella species	Yes	Yes
Salmonella non-*typhi*	No	No
Vibrio parahaemolyticus	Yes (occasionally)	No
Escherichia coli O157:H7	Yes	No
Campylobacter	Yes	Yes
Yersinia	Yes (occasionally)	Sometimes
Listeria monocytogenes	No	Yes

[a] For all organisms listed, fever is present.

The diagnosis is confirmed by isolation of the organism from contaminated food. The illness is self-limited and treatment is supportive.

KEY FACT

✓ Frequently, food poisoning due to *B cereus* has a short incubation period and is associated with ingestion of a preformed toxin (usually in fried rice)

Escherichia coli

Diarrhea caused by *E coli* can be either enterotoxigenic or enterohemorrhagic. Enterotoxigenic *E coli* is the most common etiologic agent of traveler's diarrhea. Treatment consists of fluid and electrolyte replacement along with loperamide plus a fluoroquinolone or rifaximin. Medical evaluation should be sought if fever and bloody diarrhea occur. For prophylaxis, travelers should use food and water precautions. Routine prophylactic use of antibiotics is not recommended. Use of bismuth subsalicylate as primary prophylaxis for travelers reduces the incidence of enterotoxigenic *E coli*–associated diarrhea by up to 60%.

KEY FACT

✓ Diarrhea caused by *E coli* can be enterotoxigenic or enterohemorrhagic. Enterotoxigenic *E coli* is the most common etiologic agent of traveler's diarrhea

Enterohemorrhagic *E coli* are strains capable of producing Shiga toxin. One common Shiga toxin–producing strain is *E coli* O157:H7. This agent has been identified as the cause of foodborne illness, outbreaks in nursing homes and child care centers, and sporadic cases. It also has been transmitted by eating undercooked beef and other contaminated food products. Bloody diarrhea, severe abdominal cramps, fever, and profound toxicity characterize this enterohemorrhagic illness. It may mimic ischemic colitis. In persons at extremes of age (old and young), the infection may produce hemolytic uremic syndrome and death. This organism should be considered in all patients with hemolytic uremic syndrome. Antibiotics are not known to be effective and may increase the likelihood of this syndrome.

Shigella

Diarrhea caused by *Shigella* species is often acquired outside the United States. It frequently is spread from person to person or through consumption of contaminated food or water. Bloody diarrhea is characteristic, bacteremia may occur, and fever is present. The diagnosis is confirmed by stool culture and blood culture (occasionally positive). Treatment is with ampicillin, trimethoprim-sulfamethoxazole, ciprofloxacin, or azithromycin. However, resistance to these antimicrobials has been reported. The illness may precede the onset of spondyloarthropathy (reactive arthritis) in persons with HLA-B27 and group B *Shigella flexneri*.

Salmonella

In the United States, *Salmonella* (non-*typhi*)–associated illness most commonly is caused by *Salmonella enteritidis* and *Salmonella typhimurium*. It is associated with consumption of contaminated foods or exposure to reptiles and snakes, pet turtles, ducklings, and iguanas. Large outbreaks have been associated with produce and even contaminated peanut butter—food sources previously not connected with this infection.

Salmonella infection is a common cause of severe diarrhea and may cause septicemia in patients with sickle cell anemia or AIDS. *Salmonella* bacteremia can lead to hematogenous seeding of abdominal aortic plaques, resulting in mycotic aneurysms. In *Salmonella* enteritis, fever is usually present and bloody diarrhea often absent (a characteristic distinguishing it from *Shigella* infection). The diagnosis is based on stool culture or PCR. Treatment is supportive, and most cases of *Salmonella* gastroenteritis resolve without therapy. Antibiotics may prolong the carrier state and do not affect the course of the disease. Antibiotics are used if blood cultures are positive or if the host is older (age >50 years), has valvular heart disease or severe atherosclerosis, has intravascular prosthesis, or is immunocompromised. Reactive arthritis may be a complication of this illness. Nontyphoidal *Salmonella* species may also cause UTIs. The UTIs caused by *Salmonella* occur particularly in patients who are coinfected with *Schistosoma haematobium.*

Salmonella serotype *typhi* is rare in the United States; often, it is found in travelers who have returned from endemic regions and who present with fever. Patients with typhoid fever have relative bradycardia and skin rash (macular, rose-colored spots occur in 50% of cases). Leukocyte counts may be decreased. Blood cultures usually are positive within approximately 10 days of symptom onset, whereas stool cultures become positive later. Antimicrobial resistance is increasingly common with *S typhi*.

Serious or invasive *Salmonella* infections should be treated with a third-generation cephalosporin or fluoroquinolone pending susceptibility data.

Listeria monocytogenes

Listeria monocytogenes is a motile gram-positive rod often mistaken for a diphtheroid in clinical cultures. Most often recognized as a cause of meningitis, it can be associated with food-borne diarrhea, typically acquired from processed deli meats or hot dogs consumed in the summer. The incubation ranges from 6 hours to 90 days. In most persons, febrile gastroenteritis is self-limited over 2 or 3 days. Infection can be severe and disseminate to involve multiple organs and to cause meningitis in patients with cellular immune defects (eg, those with a transplant or HIV infection, those taking corticosteroids or other immunosuppressive medications). Curiously, in pregnant women, *Listeria* can cause placental infection that may lead to fetal death or premature birth. Neonatal infection, also called **granulomatosis infantiseptica**, may result from transplacental transmission of *Listeria*. Diagnosis is made through stool or blood culture. Severe listerial infections are usually treated with ampicillin plus gentamicin.

KEY FACT

✓ *Listeria monocytogenes* can be associated with food-borne diarrhea, typically acquired from processed deli meats or hot dogs consumed in summer

Key Definition

Granulomatosis infantiseptica: *Neonatal infection resulting from transplacental transmission of Listeria.*

Vibrio Species

In the United States, consumption of raw or undercooked shellfish such as oysters is the most common source of infection with pathogenic *Vibrio* infection (eg, *Vibrio parahaemolyticus, Vibrio vulnificus*). *Vibrio parahaemolyticus* is appearing with increasing frequency in the United States along the Atlantic Gulf Coast and on cruise ships. Acute onset of explosive, watery diarrhea and fever are characteristic. The diagnosis is determined with stool culture. Disease usually manifests as self-limited enteritis, and antibiotic therapy is not required.

Cholera, a toxigenic bacterial diarrhea caused by *Vibrio cholerae*, continues to cause periodic pandemics, the most recent affecting South America and Central America, with the latest occurrence in Haiti. Cholera is rare in the United States and Canada, even among travelers. Fluid replacement therapy is the mainstay of its management. Antibiotics (eg, macrolides, tetracyclines, quinolones) administered for 1 to 3 days can shorten the duration of illness. Azithromycin (1g oral once) is probably the drug of choice.

Yersinia enterocolitica

Yersinia enterocolitica is the etiologic agent of several major clinical syndromes: enterocolitis, mesenteric adenitis, erythema nodosum, polyarthritis, reactive arthritis syndrome, and bacteremia associated with contaminated blood products. Approximately 20% of infected patients have sore throat. Infection with *Y enterocolitica* causing mesenteric adenitis can mimic acute appendicitis. Acquisition of infection is thought to be associated with eating contaminated food products. *Y enterocolitica* has been cultured from chocolate milk, meat, mussels, poultry, oysters, and cheese. Enterocolitis and lymphadenitis are usually self-limited, and antibiotic therapy is not necessary. For severe or complicated infection requiring hospitalization, a 5-day course of ciprofloxacin, trimethoprim-sulfamethoxazole, or doxycycline is effective.

KEY FACT

✓ *Yersinia enterocolitica* is the causative agent in the major clinical syndromes of enterocolitis, mesenteric adenitis, erythema nodosum, polyarthritis, reactive arthritis syndrome, and bacteremia associated with contaminated blood products

Clostridioides difficile

Clostridioides difficile (formerly known as *Clostridium difficile*) infection should be distinguished from other forms of antibiotic-associated diarrhea (ie, it causes watery stools and no systemic symptoms, with negative tests for *C difficile* toxin). Symptoms often occur after exposure to antibiotics and health care settings. Antibiotics with high biliary concentrations and broad aerobic and anaerobic activity are associated with higher risk of *C difficile* infection. This infection is more common in elderly persons and is associated with an increased morbidity rate. The disease spectrum ranges from mild diarrhea to severe, life-threatening colitis. Typical features are profuse, watery stools; crampy abdominal pain; constitutional illness; unexplained leukocytosis; presence of fecal leukocytes; and positive result of *C difficile* toxin assay. If enzyme-linked immunosorbent assay for toxin A and B detection is used alone, the sensitivity may be suboptimal. When clinical suspicion is high and the assay result is negative, PCR should be requested or empirical therapy provided. In selected cases, proctoscopy or flexible sigmoidoscopy can be used to look for pseudomembranes.

Box 49.1 • Indications for Hospitalization in *Clostridioides difficile* Infection[a]

Patient has an unstable condition and presents with the following:

- Intractable vomiting
- Dehydration
- Hypotension
- Sepsis
- Severe abdominal pain
- Bowel perforation or megacolon[b]

[a] Clinical judgment should be used when determining whether a patient's condition is unstable and whether the patient needs hospitalization. Patient should be kept in contact isolation during the hospital stay.

[b] Megacolon or bowel perforation can complicate *C difficile* infection. If a patient has abdominal distention with continued abdominal pain despite resolution of or decrease in diarrhea, a diagnosis of toxic megacolon with or without perforation should be suspected. Plain abdominal radiographs should be obtained.

Disease can be localized to the cecum (eg, postoperatively with clinical ileus) and can present as fever of unknown origin. A new toxigenic strain (North America pulsed-field type 1) associated with a binary toxin has become epidemic and is associated with fluoroquinolone resistance and more severe disease. Indications for hospitalization for *C difficile* infection are listed in Box 49.1.

KEY FACT

✓ Symptoms of *C difficile* infection often develop after exposure to antibiotics and health care facilities

Treatment of *C difficile* infection differs depending on the severity of illness and whether it is the first infection episode or recurrent disease (Table 49.6). Besides promptly initiating appropriate antimicrobial therapy directed at *C difficile*, use of unnecessary other antibiotics and acid-suppression medications (eg, proton pump inhibitors, histamine blockers) should be discontinued, and antiperistaltic agents should be avoided. Test of cure after treatment is not recommended.

KEY FACT

✓ Therapy for *C difficile* infection depends on illness severity and whether the infection is the first episode or recurrent disease

Relapse is frequent (>15% of cases) and necessitates retreatment. Recurrent *C difficile* infection is defined as symptom recurrence **and** a stool test positive for *C difficile* within 56 days of symptom resolution from the prior infection. Reinfection is defined as symptom recurrence with a stool test positive for *C difficile* beyond 56 days of symptom resolution from the prior infection. Recurrent infection should be treated in accordance with guidelines for recurrent infection; first recurrence may be treated as first episode of infection (Table 49.6).

Currently, the use of probiotics in patients with *C difficile* infection is not recommended because of insufficient evidence of efficacy and the possibility of potential harm in immunocompromised patients. In addition, no evidence shows that adding cholestyramine to the treatment regimen decreases the risk of recurrence. Moreover, cholestyramine binds to vancomycin and is contraindicated.

Total colectomy may be lifesaving in severe cases. Indications for surgical consultation include hypotension requiring vasopressor therapy, clinical signs of sepsis and organ dysfunction (renal and pulmonary), mental status changes, certain laboratory results (white blood cell count $\geq 50\times10^9$/L and lactate ≥ 5 mmol/L), and failure to improve from medical therapy after 5 days.

Fecal microbiota transplant may be helpful for patients who have refractory or symptomatically recurrent *C difficile* infection despite treatment with conventional antibiotic therapies. The transplant involves infusion of processed fecal material from a screened, approved donor to replenish the normal bacterial flora of a patient's colon. Although not approved by the US Food and Drug Administration, this procedure has been highly effective in patients with refractory and recurrent *C difficile* infection. Indications for a fecal microbiota transplant are listed in Box 49.2.

KEY FACT

✓ Fecal microbiota transplant may be helpful for refractory or symptomatically recurrent *C difficile* infection despite treatment with conventional antibiotic therapies

Viral Diarrhea

Many types of viral diarrhea can be defined by their seasonal epidemiologic factors. Rotavirus infection is the most common cause of sporadic mild diarrhea in children. It may be spread from children to adults. It usually occurs during the winter. Vomiting is a more common early manifestation than watery diarrhea. Hospitalization for dehydration is often needed for young children. Diagnosis is made with detection of antigen in stool. Treatment is symptomatic.

Noroviruses are a common cause of epidemic diarrhea and so-called winter vomiting disease in older children and adults.

Table 49.6 • Treatment of *Clostridioides difficile* Infection

Severity	**First Episode or First Recurrence**	**Second (or Subsequent) Recurrence**
Mild or moderate Diarrhea with no additional signs or symptoms of severe or severe-complicated infection	Metronidazole: 500 mg orally every 8 h for 10 d (consider change to vancomycin if no response after 5-7 d; for patients who do not tolerate or are allergic to metronidazole and for pregnant or breastfeeding women, vancomycin should be used at standard dosing)	Vancomycin: 125 mg 4 times daily for 14 d; then 125 mg 2 times daily for 7 d; then 125 mg once daily for 7 d; then 125 mg once every other d for 8 d; then 125 mg once every 3 d for 15 d
Severe (WBC count ≥15×10^9/L, creatinine ≥1.5 × baseline, or albumin <3 g/dL)	Vancomycin: 125 mg oral or NG tube every 6 h for 10 d	Vancomycin: 125 mg 4 times daily for 14 d; then 125 mg 2 times daily for 7 d; then 125 mg daily for 7 d; then 125 mg once every other d for 8 d; then 125 mg once every 3 d for 15 d
Severe-complicated[a] Any of the following attributable to *C difficile* infection: admission to ICU, hypotension, ileus or considerable abdominal distention, WBC count ≥35×10^9/L or 2×10^9/L, serum lactate levels >2.2 mmol/L, end-organ failure (eg, mechanical ventilation, renal failure; includes shock and megacolon)	Vancomycin[b]: 500 mg oral or via NG tube every 6 h for 14 d *And* Metronidazole: 500 mg IV every 8 h for 14 d	Vancomycin: 500 mg oral or via NG tube every 6 h for 14 d *And* Metronidazole: 500 mg IV every 8 h for 14 d *Then* Vancomycin: 125 mg 4 times daily for 14 d; then 125 mg 2 times daily for 7 d; then 125 mg daily for 7 d; then 125 mg once every other d for 8 d; then 125 mg once every 3 d for 15 d

Abbreviations: ICU, intensive care unit; IV, intravenously; NG, nasogastric; WBC, white blood cells.

[a] On significant clinical improvement (eg, decrease in diarrhea, improvement of vital signs, resolution of sepsis or megacolon), IV metronidazole therapy can be discontinued and treatment should be continued with oral vancomycin and a decrease in dose from 500 mg to 125 mg.

[b] If patient has ileus, vancomycin retention enemas can be considered, but they come with a risk of rectum or colon perforation. Clinician should obtain gastroenterology consult.

These viruses have high secondary attack rates. Outbreaks have been reported from day-care facilities, nursing homes, hospitals, family gatherings, and cruise ships. Various contaminated foods and liquids, such as shellfish, undercooked fish, cake frosting, salads, and water, have been implicated. The condition is explosive and self-limited (36 hours) with severe nausea, vomiting, watery diarrhea, and dehydration. Treatment is symptomatic.

Parasitic Diarrhea

The histories of travel and exposure are critical to identifying causative pathogens in parasitic diarrhea. The parasitic conditions most common in the United States are giardiasis, amebiasis, and cryptosporidiosis.

Box 49.2 • Indications for Fecal Microbiota Transplant

≥3 episodes of *Clostridioides difficile* infection

Previous treatment with first-line therapies for *C difficile* infection (vancomycin, metronidazole, or fidaxomicin)

Previous treatment of ≥1 courses of a 6- to 8-wk vancomycin treatment taper or vancomycin treatment followed by rifaximin for 2 wk

Refractory moderate to severe *C difficile* diarrhea that fails vancomycin therapy after >1 wk

Giardiasis may present with abdominal bloating, weight loss, and flatulence. Hosts at risk are men who have sex with men, hikers with exposures to fresh water streams, day-care contacts, and persons with immunoglobulin A deficiency or HIV infection. A wet-preparation examination of stool or a *Giardia* antigen test can establish the diagnosis. Treatment is with metronidazole or tinidazole.

KEY FACT

✓ Giardiasis may present with abdominal bloating, weight loss, and flatulence. Hosts at risk for giardiasis are men who have sex with men, hikers with exposures to fresh water streams, day-care contacts, and persons with immunoglobulin A deficiency or HIV infection

Entamoeba histolytica infection is acquired through ingestion of *E histolytica* cysts in contaminated water or food. Amebiasis is more common in immigrants from regions with high endemic rates of the disease, such as Central America and South America. Infected patients may present with a subacute onset of colitis or liver abscess. Diagnosis is made by stool testing for ova or by serum antibody tests. Treatment is with metronidazole (750 mg 3 times daily for 7 to 10 days). After treatment, the intestinal carrier state is eradicated with paromomycin or iodoquinol.

Cryptosporidium parvum is an important cause of diarrhea, especially in persons with AIDS, who may have a chronic, debilitating illness. Cryptosporidiosis is also a cause of self-limited diarrhea in otherwise healthy persons. Waterborne outbreaks occur most often in late summer and fall. The organism is resistant to chlorination and can best be eliminated from water sources by microfiltration. Among patients, 35% have a coinfection, most commonly with *Giardia*. The stool *Cryptosporidium* antigen test, based on enzyme-linked immunosorbent assay, has a sensitivity of 87%, a specificity of 99%, and a positive predictive value of 98%. No fully optimal therapy is available for treating *Cryptosporidium*. Nitazoxanide is the drug of choice for therapy.

Cyclospora cayetanensis is a protozoan that can cause persistent diarrhea, fever, and profound fatigue. It has been linked to consumption of contaminated food shipped to the United States. Like *Cryptosporidium*, the organism may not be detected on routine stool examinations; therefore, tests specific to the organism should be ordered (modified acid-fast stain and PCR tests). Trimethoprim-sulfamethoxazole is the preferred drug for treatment. Ciprofloxacin is an alternative treatment for patients with sulfa allergy.

Intra-abdominal Abscesses

Hepatic abscesses can be bacterial (more frequently) or nonbacterial in origin. Common nonbacterial causes include *Candida* and *E histolytica* (amebic abscess). Bacterial hepatic abscesses can be a result of portal vein bacteremia from an enteric source (such as appendicitis or diverticulitis), a biliary source, or a nonabdominal source. Fever, malaise, and abdominal pain are the usual symptoms. Computed tomography is the preferred imaging method. Causative pathogens include enteric gram-negative rods (such as Enterobacteriaceae) and anaerobes (such as *Bacteroides*). Blood cultures and amebic serologic tests are recommended for a patient's work-up. If the amebic serologic results are negative, aspiration (diagnostic and therapeutic) and culture are recommended. Therapy should be guided by culture results.

Splenic abscesses are frequently due to hematogenous seeding (eg, from endocarditis). Unexplained thrombocytosis in the clinical setting of fever should raise the concern for splenic abscess. Small abscesses (<3 cm) can be managed with percutaneous drainage and directed antimicrobial therapy. Large abscesses usually require splenectomy.

Psoas abscesses arise with the contiguous spread from perivertebral, genitourinary, or gastrointestinal foci. Hematogenous seeding occurs with *S aureus* bacteremia. The psoas muscle is also a site of tuberculous abscesses.

Pancreatic abscesses usually occur in cases of infected pancreatic necrosis. The abscesses are often polymicrobial and reflect the biliary and intestinal flora. Treatment is endoscopic or percutaneous drainage and culture-directed antimicrobial therapy.

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Skin, Soft Tissue, Bone, and Joint Infections

ERIC O. GOMEZ URENA, MD; AARON J. TANDE, MD

Skin and Soft Tissue Infections

Specific skin and soft tissue infections can be characterized by their visual appearance, including vesicles, bullae, folliculitis, crusted lesions, papular lesions, ulcerations, and cellulitis.

Nonpurulent cellulitis is an acute, spreading infection of the dermis and subcutaneous tissue. Cellulitis (Figure 50.1) is most common in tissue damaged by trauma and in extremities with impaired venous or lymphatic drainage (eg, the arm after mastectomy, the leg after saphenous vein harvest for coronary artery bypass grafting). Minor inflammation or disruption of skin integrity from tinea pedis may serve as a portal of entry for β-hemolytic streptococci (Figure 50.2). The involved area—usually on the lower extremity—is tender, warm, erythematous, and swollen. It lacks sharp demarcation from uninvolved skin. Cellulitis may recur in patients with a history of dermatitis, malignancy, or a history of ipsilateral limb cellulitis. Severe infection with group A streptococci can complicate dermatomal varicella zoster virus infection.

Key Definition

Nonpurulent cellulitis: *Acute, spreading infection of the dermis and subcutaneous tissue.*

KEY FACTS

- ✓ Cellulitis is most common in tissue damaged by trauma and in extremities with diminished venous or lymphatic drainage
- ✓ In cellulitis, minor inflammation or disruption in skin integrity from tinea pedis may serve as an entry portal for β-hemolytic streptococci

Acute purulent cellulitis is often due to community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infection. Other organisms, such as methicillin-sensitive *S aureus* or β-hemolytic streptococci, may also have a role. CA-MRSA cellulitis should be suspected in patients 1) with recurrent furunculosis, 2) with cellulitis who have a prior personal history of, a family member or close contact with, CA-MRSA, and 3) who do not respond to antimicrobial coverage for methicillin-sensitive *S aureus* and streptococci. Options for treatment in these cases include trimethoprim-sulfamethoxazole, clindamycin, or doxycycline. Use of vancomycin, daptomycin, or linezolid should be strongly considered for patients who do not respond to initial therapy with a β-lactam, who have serious illness at initial presentation, and in whom multidrug-resistant *S aureus* is suspected.

The editors and authors acknowledge the contributions of Elie F. Berbari, MD, to the previous edition of this chapter.

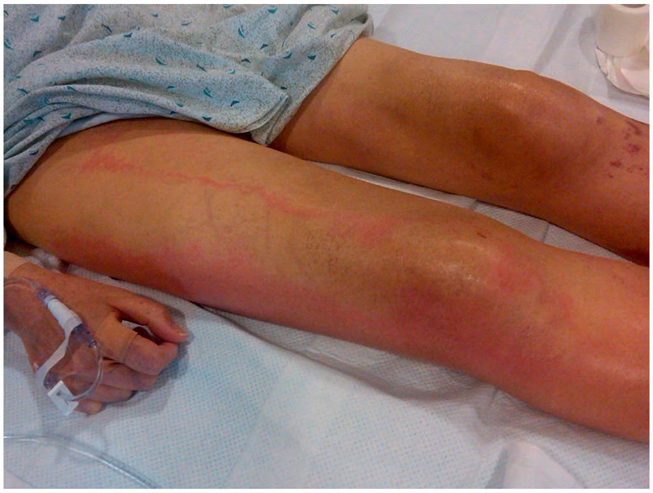

Figure 50.1. *Cellulitis With Lymphangitic Streaking due to* Yokenella regensburgei.

(From Bhowmick T, Weinstein MP. A deceptive case of cellulitis caused by a Gram-negative pathogen. J Clin Microbiol. 2013 Apr;51[4]:1320-3. Epub 2013 Jan 30; used with permission.)

KEY FACT

- ✓ Acute purulent cellulitis is often the result of CA-MRSA. Other organisms, such as methicillin-sensitive *S aureus* or β-hemolytic streptococci, may also be causes

The approach to treatment of cellulitis is guided by the type of skin and soft tissue infection and the severity of clinical presentation. Empirical antibiotic therapy should include MRSA coverage when MRSA is suspected on the basis of local epidemiologic factors and the presence of purulence. When a patient presents with a purulent lesion, it should be drained and the specimen sent for Gram stain and bacterial culture to exclude CA-MRSA.

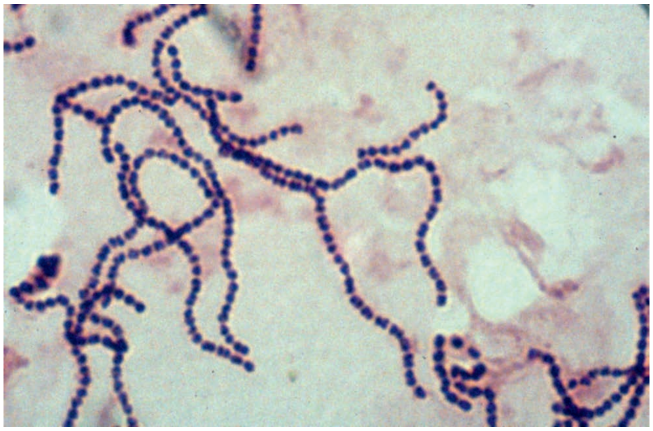

Figure 50.2. *Chaining of β-Hemolytic Streptococci in a Blood Culture (Gram Stain).*

Importantly, clinicians should exclude animal or human bites, hot-tub folliculitis, necrotizing fasciitis, fish tank or water exposures, and mixed infections in patients with diabetes mellitus. In the absence of these findings, cellulitis is most often due to β-hemolytic streptococci. A first-generation oral or parenteral cephalosporin (eg, cephalexin, cefadroxil, or cefazolin) is the usual initial choice when MRSA is not suspected.

KEY FACT

- ✓ Exclusion of animal or human bites, hot-tub folliculitis, necrotizing fasciitis, fish tank or water exposures, and mixed infections is important

Erysipelas (Figure 50.3) is a superficial cellulitis with prominent lymphatic involvement, presenting with an indurated peau d'orange appearance that has a raised border well demarcated from normal skin. This infection is painful and most often occurs in elderly persons. Recent reports have associated erysipelas with "toxic strep syndrome."

Key Definition

Erysipelas: *Superficial cellulitis with lymphatic involvement, with peau d'orange appearance and a raised border.*

KEY FACT

- ✓ A superficial cellulitis, erysipelas has prominent lymphatic involvement and presents with an indurated peau d'orange and a raised border well demarcated from healthy skin

The term *impetigo* describes a superficial skin infection. Historically, *Streptococcus pyogenes* was the most common cause of impetigo. Since the 1980s, however, most cases of impetigo have been caused by *S aureus* or mixed infections with *S aureus* and β-hemolytic streptococci.

Unusual causes of soft tissue infection include *Eikenella corrodens* and oral anaerobes after human bites (eg, knuckles cellulitis after a fist fight), *Pasteurella multocida* after cat or dog bites, *Capnocytophaga canimorsus* after dog bites, *Aeromonas hydrophila* after freshwater exposure or exposure to leeches, *Vibrio vulnificus* after salt water exposure, *Erysipelothrix rhusiopathiae* and *Streptococcus iniae* after fish exposure, and *Pseudomonas aeruginosa* after hot-tub exposure.

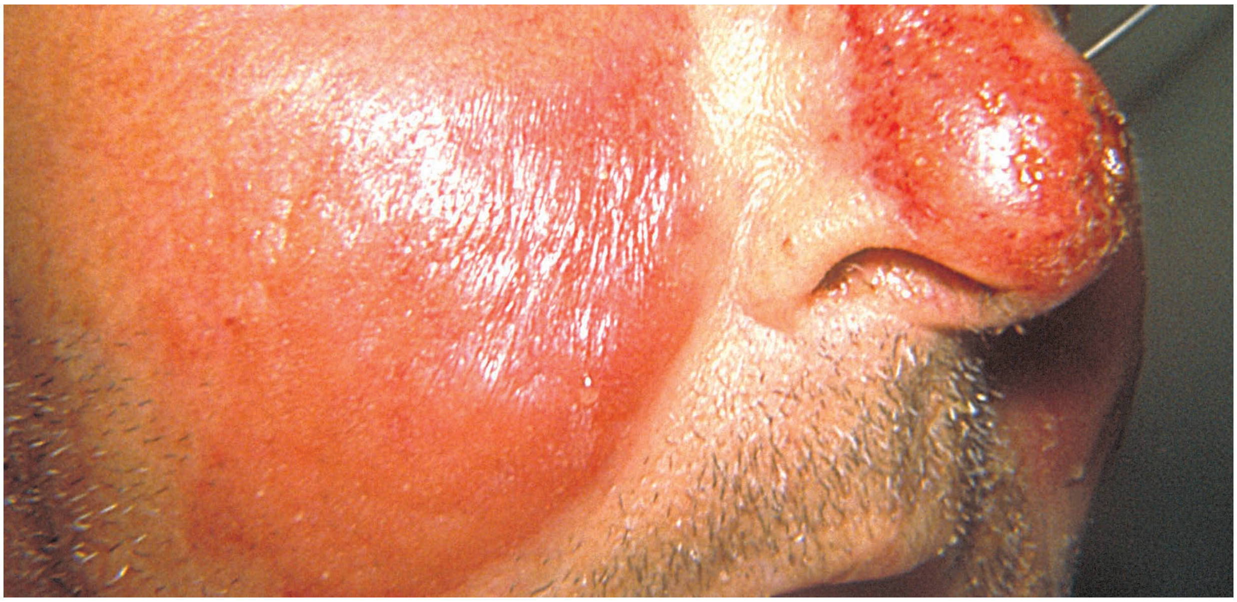

Figure 50.3. *Erysipelas.*

(Modified from Centers for Disease Control and Prevention. Facial erysipelas manifested as severe malar and nasal erythema and swelling [Internet]. Atlanta [GA]: Centers for Disease Control and Prevention; c1963 CDC/Thomas F. Sellers. Available from: http://phil.cdc.gov/phil/details.asp?pid=2874.)

Several severe complications can occur with soft tissue infections. They include necrotizing fasciitis (usually due to a polymicrobial infection or a toxin-producing group A *Streptococcus*) and pyomyositis (usually due to *S aureus*). The primary management of necrotizing infections includes prompt surgical débridement and directed antimicrobial therapy, including a protein synthesis inhibitor such as clindamycin and a β-lactam antibiotic for invasive group A streptococcal syndromes (Figure 50.2).

KEY FACT

✓ A complication of soft tissue infections is necrotizing fasciitis, usually caused by a polymicrobial infection or toxin-producing group A *Streptococcus*

The mortality rate associated with streptococcal necrotizing fasciitis is 30%, even in previously healthy patients and with appropriate treatment. Effective treatment requires early recognition of the illness, with prompt initiation of antibiotic treatment and early and aggressive surgical débridement of devitalized tissue.

KEY FACTS

✓ Streptococcal necrotizing fasciitis has a mortality rate of 30%, even in previously healthy patients and with appropriate treatment

✓ Most patients with streptococcal necrotizing fasciitis require debridement

Unlike many other pathogens, group A streptococci continue to be susceptible to the penicillins. First-generation cephalosporins and vancomycin are effective alternative drugs. Erythromycin-resistant strains have been reported, but so far they are uncommon in the United States. Evidence suggests that a protein synthesis inhibitor such as clindamycin and penicillin in combination are the most effective antibiotics for treating streptococcal necrotizing fasciitis. This may be related to the efficacy of clindamycin as a toxin-inhibiting agent and to retained efficacy in the setting of a high inoculum of organisms.

KEY FACT

✓ Evidence indicates that clindamycin and penicillin in combination are the most effective antibiotics for treating streptococcal necrotizing fasciitis

Toxic Shock Syndrome

Group A streptococci produce many disease-causing exotoxins. Scarlet fever may develop in persons with no previous immunity to erythrogenic toxin. Production of hyaluronidase causes the rapidly advancing margins characteristic of cellulitis due to β-hemolytic streptococci. Streptococcal exotoxin A has similarities to toxic shock syndrome toxin 1 produced by *S aureus*, which causes toxic shock syndrome.

Streptococcal toxic shock syndrome is similar to staphylococcal toxic shock syndrome (see below). Patients with invasive group A streptococcal infection have associated hypotension and 2 of the following: renal impairment, coagulopathy, liver impairment, adult respiratory distress syndrome, rash (which may desquamate), or soft tissue necrosis. Symptoms are caused by production of streptococcal toxin (pyrogenic exotoxin A). Most patients have skin or soft tissue infection, are younger than 50 years, and are otherwise healthy. These characteristics compare with those of patients who have invasive group A streptococcal infections without the streptococcal toxic shock syndrome. This patient group may present with only severe limb pain and no skin lesions. Most patients have bacteremia (in contrast to toxic shock syndrome due to *S aureus*).

Treatment of streptococcal toxic shock syndrome includes early administration of antibiotics, supportive care, and surgical débridement as needed. The case fatality rate is 30%. Clindamycin plus high-dose penicillin G is the preferred regimen because clindamycin may suppress exotoxin and M-protein production, in addition to its activity against group A streptococci. In severe cases, consideration should be given to the use of early intravenous immunoglobulin therapy, although the data to support this practice remain conflicting.

Staphylococcal toxic shock syndrome is caused by the establishment or growth of a toxin-producing strain of *S aureus* in a nonimmune person. Clinical scenarios associated with this syndrome include prolonged, continuous use of tampons in young menstruating women, postoperative and nonoperative wound infections, localized abscesses, and *S aureus* pneumonia developing after influenza. Staphylococcal toxic shock syndrome is a multisystem disease. Clinical criteria include fever, hypotension, erythroderma (often leads to desquamation, particularly on palms and soles), and involvement of 3 or more organ systems. Onset is acute; blood culture results are usually negative. The condition is caused by production of staphylococcal toxic shock syndrome toxin 1. Treatment includes identification and management of any focal source of infection (such as removal of tampon or incision and drainage of abscesses), culture-directed antimicrobials, and supportive care. Subsequent episodes are treated with a β-lactam antibiotic (if susceptible), which decreases the frequency and severity of subsequent attacks. The relapse rate may be as high as 40% (in menstruation-related disease). The mortality rate is 5% to 10%.

Infections Due to Other, Unusual Organisms

Pasteurella multocida

Pasteurella multocida is a common cause of acute cutaneous infection after a cat or dog bite. Soft tissue infection after a dog or cat bite should be treated with amoxicillin-clavulanate or a combination of fluoroquinolone and clindamycin to cover the pathogens in the oral flora of the biting animal and the skin flora of the infected person.

Capnocytophaga canimorsus (Formerly Called DF-2)

This organism may cause rapidly progressive soft tissue infection, bacteremia, and fulminant sepsis in asplenic persons who are bitten by domestic animals, such as dogs. Treatment of *C canimorsus* infection is with penicillins or cephalosporins.

Vibrio vulnificus

Vibrio vulnificus can cause a severe bullous soft tissue infection in persons with underlying cirrhosis or hemochromatosis. Disease is usually acquired by the ingestion of raw oysters or through injury sustained in warm salt water. Chronic liver disease predisposes to the infection. After the abrupt onset of fever and hypotension, multiple hemorrhagic bullae develop. Clinical syndromes associated with *V vulnificus* include bloodstream infection, gastroenteritis, and cellulitis. Even with prompt therapy, the mortality rate exceeds 30%. Bloodstream infection or cellulitis is treated with tetracycline, cefotaxime, ceftriaxone, or ciprofloxacin. *Vibrio vulnificus* is not uniformly susceptible to aminoglycosides.

KEY FACTS

✓ *Vibrio vulnificus* can cause a severe bullous soft tissue infection in persons with underlying cirrhosis or hemochromatosis

✓ *Vibrio vulnificus* disease is acquired usually through ingestion of raw oysters or through injury sustained in warm salt water

Bone and Joint Infections

Acute Bacterial Arthritis (Nongonococcal)

Most commonly, acute bacterial arthritis is due to hematogenous seeding of the joint and occurs in persons with underlying crystalline or rheumatoid arthritis, injection drug users, and patients undergoing hemodialysis. The hip and knee joints are the 2 most commonly involved joints. Infection is typically monoarticular, but infection involving multiple joints may occur, particularly in patients with *S aureus* bacteremia. *Staphylococcus aureus* (most frequent cause) and β-hemolytic streptococci cause the majority of cases of native joint infection, whereas *Salmonella* septic arthritis is proportionally more common in persons with sickle cell disease. Septic arthritis is due to gram-negative aerobic bacilli in 20% of cases, and this type is more common in elderly persons. By comparison, *P aeruginosa* infection is associated with injection drug use.

KEY FACTS

✓ Most commonly, acute bacterial arthritis results from hematogenous seeding of the joint and occurs in persons with underlying crystalline or rheumatoid arthritis, injection drug users, and patients undergoing hemodialysis

✓ Hip and knee joints are the most commonly involved in acute bacterial arthritis

✓ These infections are commonly caused by *S aureus* (most often) and β-hemolytic streptococci

✓ Persons with sickle cell disease may have *Salmonella* septic arthritis

✓ Septic arthritis is due to gram-negative aerobic bacilli in 20% of cases, and this type is more common in elderly persons

Clinical features of acute bacterial arthritis include fever, joint pain, and swelling. Rapid onset of a hot, swollen joint that is tender and worsened by movement is the hallmark clinical presentation of septic arthritis. In general, if the affected joint is in the lower extremity, the patient cannot bear weight on it. Pain that limits range of motion is helpful for distinguishing septic arthritis from septic bursitis. In patients with rheumatoid arthritis, the clinical presentation may be abrupt onset of a polyarticular joint flare or pain disproportionately greater than indicated by findings on the joint examination. All suspected septic joints should undergo a diagnostic arthrocentesis. Infected synovial fluid is usually turbid, and the leukocyte count generally exceeds 40×10^9/L (>75% polymorphonuclear neutrophils), but it may be lower. This condition may overlap and be confused with other inflammatory arthropathies. Gram stain is positive in approximately 50% of cases, and bacterial cultures identify a pathogen in more than 80% if specimens are obtained before antimicrobial therapy. Radiographs are not helpful in early cases because destructive changes may take up to 2 weeks to occur. Because of the progressive articular damage that occurs if acute bacterial arthritis is untreated, antimicrobial therapy should be initiated immediately after arthrocentesis and urgent orthopedic surgical consultation obtained. Empirical therapy should include agents directed against *S aureus* and aerobic gram-negative bacilli. Percutaneous, arthroscopic, or open surgical débridement is an essential part of therapy. Hip, shoulder, and sternoclavicular joint involvement, development of loculations, and persistently positive blood or joint culture are indications for arthroscopy or open surgical débridement. The duration of antimicrobial therapy is 2 to 4 weeks.

KEY FACTS

✓ A diagnostic aspiration should be performed of all septic joints in which acute bacterial arthritis is suspected

✓ The duration of antimicrobial therapy is 2-4 weeks for acute bacterial arthritis

✓ Empirical therapy for acute bacterial arthritis should include agents directed against *S aureus* and aerobic gram-negative bacilli

✓ Percutaneous, arthroscopic, or open surgical débridement is an essential part of therapy for acute bacterial arthritis

Gonococcal Arthritis

Disseminated gonococcal infection develops in approximately 0.2% of patients with genital *Neisseria gonorrhoeae* infection or asymptomatic colonization. This is the most common form of septic arthritis in sexually active persons younger than 30 years who may be asymptomatic carriers of gonococci. Risk factors for disseminated gonococcal infection include female sex, urban residence, prostitution, intravenous drug use, and low socioeconomic status.

There are 2 main clinical presentations. The more common presentation involves the classic triad of dermatitis manifested by a vesiculopustular or pustular rash, tenosynovitis, and migratory polyarthritis, which may be accompanied by fever. Skin lesions may be tiny papules with an erythematous base and a hemorrhagic or necrotic center, occurring anywhere on the extremities. The second clinical presentation involves a monoarthritis, usually of the knee, wrist, or ankle. These 2 patterns may overlap. Women present with gonococcal arthritis commonly during pregnancy or within 1 week after onset of menses, possibly related to the change in the pH of vaginal secretions. Extra-articular complications of disseminated gonococcal infection include meningitis, myopericarditis, and sepsis.

If there is suspicion for gonococcal infection, specimens from the pharynx, joints, rectum, blood, and genitourinary tract should be obtained and tested either with culture-based methods using specialized media or using nucleic acid amplification tests if available. Synovial fluid cultures are positive in only 30% to 50% of patients with known disseminated gonococcal infection. Culture of a skin lesion is positive for gonococcus in 40% to 60% of patients with disseminated gonococcal infection.

First-line antibiotic therapy for gonococcal arthritis is intravenous ceftriaxone. Because of the increasing prevalence of fluoroquinolone-resistant gonococcus, susceptibility testing should be performed before considering completion of therapy with an oral fluoroquinolone. Treatment typically is given in a 7- to 14-day course. Approximately 30% to 50% of patients infected with *N gonorrhoeae* have a *Chlamydia* co-infection, necessitating the use of empirical azithromycin or doxycycline. It is recommended that a patient's sexual partner(s) also be treated empirically for gonorrhea and chlamydial infection. Patients who have recurrent infections may have a congenital terminal complement component deficiency (C5-C9).

KEY FACTS

- ✓ Disseminated gonococcal infection commonly presents as the classic triad of dermatitis (vesiculopustular or pustular rash), tenosynovitis, and migratory polyarthritis
- ✓ First-line antibiotic therapy for gonococcal arthritis is intravenous ceftriaxone followed by an oral fluoroquinolone, if susceptible

Rheumatic Fever and Post-streptococcal Reactive Arthritis

Arthritis affects 75% of patients with rheumatic fever. Joint involvement is more common in children. One-third of patients with acute rheumatic fever have no obvious antecedent pharyngitis. In adults, arthritis may be the only clinical feature of acute rheumatic fever. The arthritis may be migratory, with each joint remaining inflamed for approximately 1 week before another joint becomes inflamed. Monoarthritis of the knee or ankle may be present in up to 25% of patients. The arthritis of rheumatic fever is nonerosive and the synovial fluid is sterile. Jaccoud arthropathy is a rare manifestation of arthritis, characterized by ulnar deviation of the metacarpophalangeal joints with hyperextension of the proximal interphalangeal joints as a result of tendon laxity rather than bony damage. This form of arthropathy also occurs in patients with systemic lupus erythematosus. Rheumatic fever is often diagnosed with streptococcal antibody tests such as antistreptolysin O and anti-DNase B. Antibody levels peak about 4 weeks after the pharyngeal infection and then decrease over 6 months.

Antimicrobial therapy should be initiated for all patients with streptococcal pharyngeal infection. Patients with joint symptoms without carditis may be treated with high-dose salicylate therapy (3-4 g daily). Monitoring for adverse effects, such as nausea, vomiting, and gastrointestinal bleeding, is advised. Corticosteroids may be required if patients do not respond to salicylates. Joint symptoms may rebound when anti-inflammatory therapy is discontinued.

KEY FACT

- ✓ Rheumatic fever is often diagnosed with streptococcal antibody tests (eg, antistreptolysin O, anti-DNase B)

Viral Arthritis

Viruses associated with arthritis are HIV, parvovirus B19, hepatitis B, hepatitis C, rubella, adenovirus and, less commonly, mumps. Among travelers, chikungunya and Ross River virus are important causes of viral arthritis. The common clinical features of viral arthritis are acute onset of a polyarthritis with rash and fever, often self-limited. The pathogenesis involves an immune complex–mediated mechanism or direct viral infection of synovial cells. Most viral arthritides are self-limited, but a chronic arthropathy may occur, notably after infection with parvovirus B19 and chikungunya virus.

KEY FACTS

- ✓ The common clinical features of viral arthritis include acute onset of a polyarthritis with accompanying rash and fever, often self-limited
- ✓ Parvovirus B19 and chikungunya virus can cause a chronic arthropathy

Chronic Monoarticular Arthritis

Tuberculosis and the nontuberculous mycobacteria should be considered in patients presenting with insidious-onset arthritis and chronic arthritis. Although historically uncommon in the United States, mycobacterial joint infections are increasingly being recognized in immunocompromised patients and persons who emigrated from countries with a high burden of tuberculosis. Musculoskeletal involvement occurs in approximately 1% to 2% of patients with tuberculosis; the majority of these patients also have pulmonary tuberculosis. Tuberculous septic arthritis often presents as an indolent, monoarticular infection affecting a large joint, such as the knee or hip, as a result of contiguous spread from an adjacent bone infection. *Mycobacterium marinum* lives in saltwater or freshwater. Patients may become infected from direct skin inoculation by handling marine life or through exposure of non-intact skin to water sources. Clinical features may include nodular skin lesions or a cellulitic involvement at the area of inoculation, accompanied by an inflammatory arthritis or tenosynovitis frequently involving the hand and wrist.

Fungal joint infections are often difficult to diagnose unless there is a strong suspicion they are present. Clinical symptoms are variable and may include migratory arthralgias, tenosynovitis, or monoarthritis. Symptoms may be present for several weeks to months before diagnosis. The endemic mycoses, such as *Histoplasma, Blastomyces, Coccidioides*, and *Sporothrix* species, may cause disease in anyone experiencing a compatible exposure; a detailed exposure history may prove invaluable. In contrast, infection with *Cryptococcus* or *Aspergillus* species occurs most commonly among immunosuppressed patients. Sporotrichosis and blastomycosis are the fungal infections most likely to have musculoskeletal manifestations. The classic presentation in sporotrichosis is a gardener or farmer with a rose-thorn penetration that results in a papular, ulcerative rash at the site of inoculation, with lymphatic spread and tenosynovitis or monoarthritis. Blastomycosis of the bone resembles osteolytic lesions with a periosteal reaction reminiscent of a bone tumor. Definitive diagnosis is made by culturing the causative organism from sterile culture, but serologic evidence of infection may help support a clinical diagnosis if culture results are negative.

In patients with chronic monoarticular arthritis of the knee and a history of tick exposure, positive Lyme serologic findings, or erythema migrans, clinicians should consider a diagnosis of chronic Lyme arthritis.

KEY FACTS

- ✓ Tuberculosis and the nontuberculous mycobacteria should be considered in patients presenting with insidious-onset arthritis and chronic arthritis, particularly with epidemiologic risk factors for tuberculosis
- ✓ An exposure history for *Mycobacterium marinum*, the endemic mycoses, or Lyme disease may help guide further evaluation for these organisms

Prosthetic Joint Infection

Infection of joint prostheses occurs in 1% to 3% of joint replacements. The clinical manifestations of prosthetic joint infection (PJI) vary widely. Infection early after joint replacement may present with signs and symptoms of surgical site infection, often accompanied by systemic symptoms of infection such as fever. In contrast, delayed infection due to less virulent pathogens such as coagulase-negative staphylococci or *Cutibacterium acnes* (formerly *Propionibacterium acnes*) may present with persistent pain without systemic symptoms. Plain radiographs may show loosening of the prosthesis or lucency at the bone-cement interface.

The diagnosis of PJI may be confirmed from the presence of a sinus tract leading from the skin to the prosthesis, the growth of a pathogen from multiple periprosthetic specimens, or a combination of supportive findings. The microbiologic findings of PJI depend on the duration since surgery and the joint involved. Early after surgery, more virulent pathogens such as *S aureus* and aerobic gram-negative bacteria are common. Delayed infections, occurring 3 to 12 months after surgery, are often caused by coagulase-negative staphylococci. Late-onset acute hematogenous infection is most commonly caused by *S aureus*. Accurate microbiologic diagnosis of PJI is critical to successful management, and antimicrobials should be withheld until surgery, unless the patient has signs of systemic infection.

PJI always requires a combined medical and surgical effort. Chronic PJI (symptoms for longer than 3 weeks) is optimally managed with complete resection of the prosthesis and replacement either during the same surgery (1-stage approach) or in a delayed approach (2-stage approach). Antimicrobial treatment is typically given for 4 to 6 weeks in the setting of a 2-stage approach, but it is more nuanced in the setting of a 1-stage approach. For patients with acute PJI, satisfactory soft tissue conditions, and a well-fixed implant, treatment includes débridement and retention of the prosthesis. These patients typically receive intravenous antimicrobials for several weeks, followed by chronic oral antimicrobial therapy in an attempt to suppress the bacteria that reside within the biofilm attached to the retained prosthesis.

KEY FACTS

- ✓ The clinical manifestations of PJI may range from surgical site infection with systemic symptoms to chronic pain
- ✓ Accurate microbiologic diagnosis is essential to management of PJI, and antimicrobials should be withheld before surgery, unless there is systemic infection
- ✓ Successful management of PJI always requires a combined medical and surgical strategy

Osteomyelitis

Osteomyelitis can be a result of hematogenous seeding, contiguous spread of infection to bone from adjacent soft tissues and joints, or direct inoculation of infection into the bone due to trauma or a surgical procedure. Acute hematogenous osteomyelitis is usually monomicrobial, whereas osteomyelitis due to contiguous spread or direct inoculation is usually polymicrobial. Acute hematogenous osteomyelitis is more common in children, but it can occur in adults who have prolonged bloodstream infection, are intravenous drug users, are receiving dialysis, or have sickle cell disease. In adults, vertebral osteomyelitis is the primary manifestation of hematogenous osteomyelitis (discussed later in this chapter). *Staphylococcus aureus*, coagulase-negative staphylococci, and aerobic gram-negative bacilli are the most common organisms in acute osteomyelitis. In long bone involvement, the acute onset of pain and fever is typical. In vertebral osteomyelitis, pain may be the sole characteristic. To establish the diagnosis, clinicians may use compatible imaging changes and image-guided bone biopsy for culture and pathologic examination. Results of blood culture may be positive for a microbial cause. Specific parenteral antibiotic therapy is used for 4 to 6 weeks on the basis of culture and sensitivity test results. Surgical débridement in acute hematogenous osteomyelitis is often not necessary unless a sequestrum is present or in cases of neurologic compromise.

Chronic, contiguous osteomyelitis more commonly occurs in adults, particularly when wounds, vascular insufficiency, and diabetic foot ulcers are present. The infections are usually mixed, but *S aureus* is the single most commonly isolated organism. In the presence of foreign bodies (such as plate, screws, or prosthetic joint), coagulase-negative staphylococci are often the culprit. Local pain, tenderness, erythema, and draining sinuses are common. Fever is atypical unless concurrent cellulitis is present. Compatible radiographic changes (often vague) and bone biopsy for culture and pathologic examination are used to establish the diagnosis. Blood culture results are rarely positive. Adequate débridement, removal of dead space and foreign bodies, soft tissue coverage, and fixation of infected fractures are essential. Specific parenteral antibiotic therapy is given for 4 to 6 weeks. If a foreign body is retained in patients with staphylococcal osteomyelitis, a rifampin-based combination therapy improves outcomes. Prolonged oral antibiotic suppression may be needed with foreign body retention.

KEY FACTS

- ✓ Chronic, contiguous osteomyelitis occurs more commonly in adults than children, particularly when traumatic wounds, vascular insufficiency, and diabetic foot ulcers are present
- ✓ Chronic contiguous osteomyelitis is usually a polymicrobial infection, but *S aureus* is the single most commonly isolated organism
- ✓ When a patient with osteomyelitis has an imbedded foreign body (eg, bone plate, screws, prosthetic joint), coagulase-negative staphylococci are often the culprit bacteria

Diskitis and Vertebral Osteomyelitis

Infections of the intervertebral disk and the adjacent vertebrae may occur with or without associated epidural or psoas abscesses. These infections most often arise from hematogenous dissemination of infection from the skin and soft tissues, genitourinary tract, infective endocarditis, infected intravenous sites, injection drug use, or respiratory tract infection. The incidence is greatest among male patients, peaks in the fifth decade of life, and is increasing, particularly among the elderly population. Additional risk factors for spine infections include immunocompromised conditions, diabetes mellitus, intravenous drug use, renal failure, bacteremia, malignancy, long-term corticosteroid use, intravascular devices, and recent instrumentation or spine surgery.

The clinical presentation of vertebral osteomyelitis includes localized insidious pain and tenderness in the spine area in 90% of cases. Most commonly affected is the lumbar or lumbosacral region; cervical disease may occur in patients with head and neck infections or in injection drug users. Fever is present in less than half of cases. Because of the clinical uncertainty, a delay in diagnosis of weeks to months often occurs, which can lead to motor and sensory deficits in 15% of patients. The erythrocyte sedimentation rate is increased in more than 90% of cases, and the leukocyte count is increased in less than 50%.

KEY FACT

- ✓ Clinical presentation of vertebral osteomyelitis includes localized insidious pain and tenderness in the spine area

Plain radiography may show vertebral end-plate irregularity at 2 to 8 weeks after the onset of symptoms, but it is neither sensitive nor specific. Gadolinium-enhanced magnetic resonance imaging is the most useful test for diagnosis because of its high sensitivity (96%) and high specificity (94%) (Figure 50.4).

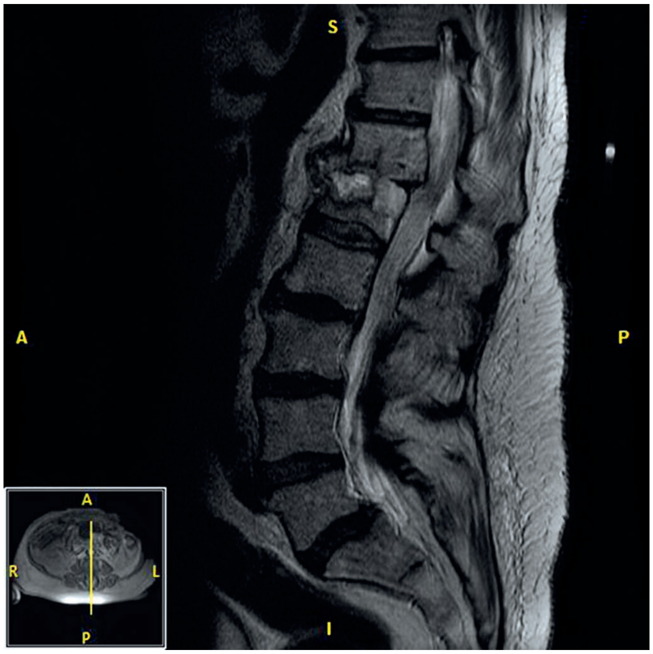

Figure 50.4. Magnetic Resonance Imaging of the Spine Showing T2 Images of a T12-L1 Disk Space Infection and Associated Contiguous Vertebral Body Involvement. Of note, image shows complete destruction of vertebral end plates. A indicates anterior; I, inferior; L, left; P, posterior; R, right; S, superior.

In patients who cannot undergo magnetic resonance imaging, computed tomography or nuclear scanning may help establish the diagnosis. The best nuclear study for imaging disk space infections is scanning with technetium combined with gallium citrate. Computed tomography–guided percutaneous aspiration or biopsy is often used to identify the causative organism, unless blood cultures identify a compatible pathogen, such as *S aureus* or *Brucella* species. If the initial result is negative, the test should be repeated before proceeding to an open biopsy procedure.

KEY FACT

- ✓ Gadolinium-enhanced magnetic resonance imaging is the most useful test for diagnosis of vertebral osteomyelitis because it provides high sensitivity (96%) and high specificity (94%)

Staphylococcus aureus and coagulase-negative staphylococci are the most common microorganisms cultured in vertebral osteomyelitis. *Mycobacterium tuberculosis* and *Brucella* are common in endemic regions. Most patients can be treated conservatively with antimicrobials. Antibiotics should be given parenterally for a minimum of 4 to 6 weeks or given longer when the patient has extensive vertebral destruction or undrained infected collections. Surgical interventions are limited to cases with progressive neurologic deterioration, spinal instability, progressive epidural abscess, or failed medical therapy.

KEY FACTS

- ✓ *Staphylococcus aureus* and coagulase-negative staphylococci are the microorganisms most commonly cultured in vertebral osteomyelitis
- ✓ In most patients, vertebral osteomyelitis can be managed conservatively with antimicrobials given parenterally for a minimum of 4-6 weeks
- ✓ Surgical interventions are limited to cases with progressive neurologic deterioration, spinal instability, progressive epidural abscess, or unsuccessful medical treatment

VII Questions and Answers

Questions

Multiple Choice (Choose the best answer)

VII.1. A 67-year-old man with a history of diabetes mellitus type 2 is admitted from the emergency department in July for new-onset headache and vomiting. Medications include metformin, lisinopril, and as-needed acetaminophen. He was well until this morning and was brought in by his roommate. On examination, his temperature is 40.1°C, heart rate is 130 beats per minute, and blood pressure is 94/60 mm Hg. Nuchal rigidity is noted, but there are no localizing neurologic findings, and he is able to follow commands. Notable laboratory results are as follows: white blood cells, 290×10^9/L; platelets, 100×10^9/L; and creatinine of 1.8 mg/dL. What is the best option in the management of this patient?

a. Blood cultures; empirical therapy with ceftriaxone, vancomycin, ampicillin, and dexamethasone, followed by computed tomography (CT) of the head and lumbar puncture (LP) if there are no radiographic contraindications
b. CT of the head, followed by LP if there are no contraindications and then empirical therapy with ceftriaxone, vancomycin, ampicillin, and dexamethasone
c. Blood cultures, LP, and then empirical therapy with ceftriaxone, vancomycin, ampicillin, and dexamethasone
d. Blood cultures, LP, and then empirical therapy with meropenem, vancomycin, and dexamethasone

VII.2. A 64-year-old woman with a history of rheumatoid arthritis presents to the emergency department with a 4-day history of fevers and malaise. She was admitted to the hospital. On day 2 of hospitalization, her blood culture results are notable for methicillin-susceptible *Staphylococcal aureus* (MSSA). She denies any localizing symptoms at the time of hospitalization. Transesophageal echocardiography (TEE) is negative for infectious endocarditis, and she is dismissed receiving cefazolin intravenously for management of her bacteremia until blood culture results are negative. Four days later, at the post-hospital follow-up appointment, she confirms resolution of fever but describes new lower back pain that she is attributing to inactivity and her rheumatoid arthritis given that she has not been taking her methotrexate and was weaned from prednisone. On physical examination, she has notable weakness of the right hip flexors and localizable pain to the mid-lower back with palpation. What is the best next step in evaluation of the patient?

a. Add vancomycin to the cefazolin therapy.
b. Order magnetic resonance imaging (MRI) of the lumbar spine.
c. Restart oral prednisone and methotrexate therapy.
d. Repeat TEE.

VII.3. A 29-year-old previously healthy man is admitted for headache that has been worsening for the past 3 days. His family provides a history of a 3-week course of upper respiratory tract symptoms, including nasal congestion and mucopurulent drainage. He was evaluated at an urgent care clinic on 2 occasions, and conservative management for a likely viral illness was recommended both times. The family provides a history of fevers being present when his nasal congestion symptoms started, but the fevers seemed to subside. During the past 3 days, as the patient's headache considerably worsened, these fevers returned. His headache at times feels global, but it is primarily localized to the right frontal area. On examination, he appears uncomfortable and has pain on palpation of the right frontal and maxillary sinuses. Computed tomography of the head confirms your suspicion of brain abscess on the right. Empirical antimicrobial coverage should include activity against which pathogens?

a. *Streptococcal* species
b. *Escherichia coli*
c. *Pseudomonas aeruginosa*
d. *Candida albicans*

VII.4. A 37-year-old woman accompanies her husband to see his physician, who has been treating the husband's HIV infection. The patient is receiving antiretroviral therapy with dolutegravir, abacavir, and lamivudine. His wife has heard about pre-exposure prophylaxis (PrEP) and would like to know more about it. She herself is healthy; her HIV test result a year ago was negative. Which of the following statements is an appropriate response to the wife?

a. PrEP is not indicated for heterosexual women.
b. She can receive PrEP without further testing.

c. She should be prescribed the same antiretroviral regimen as her husband.
d. She may be an appropriate candidate for PrEP but needs to undergo further evaluation and testing.

VII.5. A 28-year-old man presents with fever and a diffuse, erythematous maculopapular rash of 2 days in duration. He reports multiple sexual partners, including casual sex without condoms about 3 weeks ago. He has been otherwise healthy and takes no medications. He works as a school teacher. On physical examination, he has fever, a rash over his trunk, and bilateral cervical lymphadenopathy. What is the next best step in management?

a. Epstein-Barr virus serologic testing
b. A pre-exposure prophylaxis regimen
c. HIV antigen-antibody combined immunoassay
d. HIV-1 nucleic acid testing

VII.6. In a 35-year-old man, HIV infection is diagnosed through screening. He has no symptoms, has no other illnesses, and is not taking any medications. His vital signs include a temperature of 36.8°C, blood pressure of 122/70 mm Hg, heart rate of 92 beats per minute, and respiratory rate of 20 breaths per minute. Results of physical examination are unremarkable. His laboratory results are shown in Table VII.Q6.

Table VII.Q6.

Measure	Value
White blood cells	8.8×10^9/L
Hemoglobin	13.8 g/dL
Platelet count	260×10^9/L
Serum aspartate aminotransferase	38 U/L
Serum alanine aminotransferase	46 U/L
CD4+	820/mcL
HIV RNA	15,000 copies/mL

The patient wants to know whether he should be receiving antiretroviral therapy. Which of the following is the best management plan?

a. No antiretroviral therapy is indicated because the CD4 cell count is high.
b. No antiretroviral therapy is indicated because the HIV RNA level is low.
c. Trimethoprim-sulfamethoxazole therapy should be given as prophylaxis for *Pneumocystis* pneumonia.
d. Combination antiretroviral therapy should be given.

VII.7. A 65-year-old man with acute myelogenous leukemia is hospitalized to receive induction chemotherapy with cytarabine and daunorubicin. During week 3 of hospitalization, at day 9 of absolute neutropenia (absolute neutrophil count, 100 cells/mm^3), his temperature is 38.7°C. His current medications include antimicrobial prophylaxis with levofloxacin, posaconazole, and acyclovir. On evaluation, he is febrile, hypotensive, and tachycardic. Blood specimens are collected for culture, he is resuscitated with intravenous fluids, and empirical intravenous cefepime therapy is initiated. He denies any abdominal pain, diarrhea, cough, headache, or changes in the skin. He has a tunneled central catheter in the right side of the neck without any surrounding abnormalities, erythema, or tenderness on examination. He has had increased painful oral mucosal sloughing during the past 3 days. What is the best statement regarding choice of initial empirical antimicrobials for this patient?

a. Current empirical therapy should be continued while blood culture results are pending.
b. Intravenous vancomycin should be added because of the presence of a central intravascular catheter.
c. Intravenous vancomycin should be added because of the presence of hemodynamic instability.
d. Intravenous liposomal amphotericin B should be added.

VII.8. A 74-year-old man with a recent diagnosis of granulomatosis with polyangiitis and pulmonary involvement presents with severe right upper quadrant pain. Rituximab therapy was started 2 months ago when he presented with hemoptysis. His pretreatment serologic results are shown in Table VII.Q8A.

Table VII.Q8A.

Measure	Result
Hepatitis A immunoglobulin antibody	Positive
Hepatitis C antibody	Negative
Hepatitis B surface antigen	Negative
Hepatitis B surface antibody	Negative

He recalls a previous hepatitis A vaccination but not hepatitis B vaccination. He has no history of intravenous drug use or alcohol use and denies any international travel or known contacts with persons with tuberculosis. Computed tomography of the abdomen and pelvis shows no acute abnormalities. Laboratory tests results are shown in Table VII.Q8B.

Table VII.Q8B.

Measure	Value
Alanine aminotransferase	2,000 U/L
Aspartate aminotransferase	3,000 U/L
Alkaline phosphatase	300 U/L
Total bilirubin	6 mg/dL

Abdominal ultrasonography shows no biliary ductal dilatation or portal venous thrombosis. Computed tomography of the chest shows considerable improvement from prior imaging. What is the most likely diagnostic test to identify the cause of this patient's presentation?

a. Hepatitis C antibody with reflex hepatitis C RNA
b. Hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody, and hepatitis B DNA
c. QuantiFERON-TB Gold (QIAGEN)
d. Hepatitis A immunoglobulin M

VII.9. A 24-year-old man who received a kidney from a living-related donor 8 months previously is evaluated in the primary care clinic for a 5-week history of loose watery stools (average, 8 episodes per day) associated with weight loss. His current medications include tacrolimus, prednisone, and mycophenolate mofetil, and he has finished his antimicrobial prophylaxis. His pretransplant evaluation noted the following: donor positive for cytomegalovirus (CMV) and recipient negative, donor positive for Epstein-Barr virus (EBV) and recipient negative. As part of his evaluation, he was tested for *Clostridioides difficile* (formerly known as *Clostridium*) with polymerase chain reaction assay, followed by a gastrointestinal multiplex panel with polymerase chain reaction assay; results were negative. He recalls some myalgia and intermittent fever during this illness and describes a 10-lb weight loss. He denies any unusual food exposures and has been careful to ensure food is washed, cooked, and pasteurized before consumption. What is the best next step in evaluation of this patient's persistent diarrhea?

a. Colonoscopy with random biopsy
b. Polymerase chain reaction assay for EBV
c. Routine bacterial blood cultures
d. Serologic testing for CMV

VII.10. A 64-year-old man has herpes zoster involving his right flank. He is seen at day 3 of the rash onset when his lesions are crusted over and pain is improving. He asks about returning to his office-based position at work. Which of the following recommendations is the best advice for this patient?

a. He is no longer considered infectious and can return to work.
b. He should avoid returning to work because he may still spread the infection to his coworkers through respiratory droplets.
c. If his coworkers include anyone who is immunocompromised, he should not return to work as long as the lesions are present.
d. He can return to work only if oral valacyclovir therapy has been started.

VII.11. A 24-year-old avid hiker from Minnesota requests evaluation of a newly identified rash on his left thigh. The rash is erythematous, round, and warm, and there is minimal central clearing. He was examined 2 days earlier in an urgent care clinic and was given oral cephalexin for cellulitis, but the rash has not responded thus far. He feels well otherwise, and there is no visible abscess or purulent drainage. He denies any tick or mosquito bites on his recent hiking trip. What is the next best step in management of this patient?

a. Treat with oral trimethoprim-sulfamethoxazole now.
b. Test for Lyme disease now; if the result is positive, treat with doxycycline.
c. Treat with oral doxycycline now.
d. Treat with oral clindamycin now.

VII.12. A 19-year-old previously healthy woman is admitted with a 6-day acute illness that includes increased temperature (reaching 104°F), malaise, and cervical-axillary lymphadenopathy. At an outpatient visit, initial management included close observation and recommended aggressive hydration. A mononucleosis spot test was also done, and the result was positive. Because of persistent fevers and clinical worsening, she was hospitalized. At admission, laboratory results were concerning for leukopenia and relative lymphocytosis. Her platelet count was low (35×10^9/L), alanine aminotransferase and aspartate aminotransferase levels were both at 3 times the upper limit of normal, and the creatinine level was normal. On examination, she looked very ill but had no localizing pain or discomfort. The day after admission, she was transferred to the intensive care unit because of fevers and tachycardia. Blood test results were notable for worsening cytopenias: hemoglobin 9.1 g/dL and platelet count 12×10^9/L. The ferritin level was increased (6,000 mcg/L), the lactate dehydrogenase level was abnormal (>280 U/L), and mild hypertriglyceridemia was present. Blood culture results remained negative, and the HIV screening result was negative. Computed tomography of the abdomen and pelvis confirmed splenomegaly, although the liver size was within normal limits. Chest radiography showed no pulmonary infiltrates. What is the most important next step in management of this patient?

a. Perform exploratory laparotomy for evaluation of missed splenic rupture.
b. Determine HIV viral load.
c. Order an Epstein-Barr virus DNA test, a bone marrow biopsy, and hematology consultation.
d. Order an excisional lymph node biopsy and hematology consultation.

VII.13. A 75-year-old man is admitted to a general medicine service with persistent fevers, chills, and body aches. He was seen by his primary care provider about 2 days before admission. At that time, blood cultures were positive for *Enterococcus faecalis*. Given the positive blood cultures, he was directly admitted. He has a history of a bicuspid aortic valve, and a harsh blowing systolic murmur is appreciated in the right second intercostal space. Blood cultures are repeated, therapy with intravenous antibiotics is started, and transesophageal echocardiography (TEE) is performed. TEE shows a bicuspid aortic valve with degenerative changes but no vegetations or evidence of infective endocarditis. What is the next best step in management?

a. Positron emission tomography (PET) with computed tomography (CT)
b. Repeat TEE in 3 to 5 days.
c. Cardiac magnetic resonance imaging (MRI) and transthoracic echocardiography (TTE)
d. No further testing is needed; endocarditis is ruled out.

VII.14. A 48-year-old woman presents as a new patient. She is well and comes in to establish care because she recently moved into town. She states that she has a history of mitral valve prolapse with regurgitation, obesity, hyperlipidemia, and type 2 diabetes mellitus that is well controlled with metformin. She has a dental appointment tomorrow for a tooth extraction and cleaning and asks whether she needs to take any antibiotics. She recalls taking them for many years but has not been to the dentist in the past 10 years. What should be recommended to the patient?

a. Yes, take oral amoxicillin 2 g 1 hour before the dental procedure.
b. Yes, take oral clindamycin 600 mg 1 hour before the dental procedure.
c. No, antibiotics are not recommended before dental procedures.
d. Yes, take oral amoxicillin only if bleeding is anticipated from the dental procedure.

VII.15. A 62-year-old healthy man with no clinically significant medical history is admitted to the hospital after falling on the ice and sustaining a left femur fracture. He was taken directly to the operating room for open reduction and internal fixation with the placement of a plate and 4 screws. He was intubated for the procedure only. He is otherwise feeling well and is without fever, chills, nausea, chest pain, or diarrhea. On postoperative day 3, he has development of fevers, productive cough with green sputum, chills, and shortness of breath, especially with activity during physical therapy. Chest radiography shows a left lobar consolidation that is concerning for pneumonitis. He responds well to supplemental nasal cannula oxygenation at 2 L/min and is normotensive. According to the hospital's antibiogram, the rate of methicillin-resistant *Staphylococcus aureus* (MRSA) is 33%. The patient has not received any intravenous antibiotics in the past 90 days and is not at high risk for mortality. Sputum is obtained for cultures, and intravenous antibiotic therapy is started. According to current guidelines, what is the recommended empirical therapy?

a. Intravenous (IV) vancomycin, cefepime, and levofloxacin
b. Intravenous (IV) meropenem
c. Intravenous (IV) vancomycin and cefepime
d. Intravenous (IV) vancomycin, piperacillin-tazobactam, and meropenem

VII.16. A 67-year-old woman with type 2 diabetes mellitus presents to her primary care provider with 3 days of progressive fever, chills, and cough productive of green sputum. She is alert and oriented. Her vital signs are as follows: temperature, 38.5°C; respiratory rate, 35 breaths per minute; blood pressure, 110/85 mm Hg; and heart rate, 75 beats per minute. Chest radiography shows a right lower lobe consolidation. Laboratory results are as follows: white blood cells, 15×10^9/L; serum urea nitrogen, 25 mg/dL; and creatinine, 1.5 mg/dL. What is the best management strategy?

a. Outpatient treatment with oral cefdinir and azithromycin
b. Outpatient treatment with oral levofloxacin
c. Inpatient treatment with intravenous ceftriaxone and azithromycin
d. Inpatient treatment with intravenous ciprofloxacin

VII.17. A tuberculin skin test with resultant 6 mm of induration is considered positive for the diagnosis of latent tuberculosis infection in which of the following patients?

a. A 54-year-old woman, native to the United States, who has rheumatoid arthritis controlled with infliximab
b. A healthy 35-year-old man, native to the United States, who works as a microbiology technician
c. An asymptomatic 26-year-old woman who is seen in a refugee clinic, having recently arrived from South Sudan
d. A 67-year-old man, native of Canada, with severe chronic obstructive pulmonary disease

VII.18. A 53-year-old man with alcohol use disorder is hospitalized in the medical intensive care unit for fever and respiratory failure. On computed tomography, a consolidative infiltrate in the right lower lobe is suggestive of a right lower lobe abscess and right-sided empyema. Which of the following is the most likely microbiologic cause in this case?

a. *Nocardia asteroides*
b. *Klebsiella pneumoniae*
c. *Legionella pneumophila*
d. *Staphylococcus aureus*

VII.19. A 23-year-old woman with no medical history presents with urinary frequency, burning with urination, and suprapubic discomfort. She has no history of urinary tract infections. She has no fever, flank pain, nausea, or vomiting. On physical examination, she has mild suprapubic tenderness and no costovertebral angle tenderness. Results of urinalysis are 2+ leukocyte esterase and 2+ nitrites. What is the best step for treatment in this patient?

a. Ciprofloxacin 500 mg orally twice a day for 7 days
b. Clindamycin 150 mg orally 3 times a day for 3 days
c. Amoxicillin 500 mg orally 3 times a day for 3 days
d. Nitrofurantoin 100 mg orally twice a day for 5 days

VII.20. An 81-year-old woman with hypertension and type 2 diabetes mellitus fell while walking on an icy sidewalk and sustained a hip fracture. Three days postoperatively, delirium developed. The physician attending her overnight ordered blood cultures, a urine culture, and a chest radiograph because he was concerned about an infection causing delirium. A Foley catheter was in place when the urine specimen was obtained. The patient had been afebrile for her entire hospital course. Two days later, the urine culture result was positive for more than 100,000 colonies of vancomycin-resistant *Enterococcus faecium*. Urinalysis was not done. The patient is lucid during evaluation. She denies urinary frequency, dysuria, or urgency. What is the best step for treatment in this patient?

a. Linezolid 600 mg orally twice daily for 7 days
b. Daptomycin 5 mg/kg intravenously for 7 days
c. Fosfomycin 3 g sachet orally for 1 dose
d. No antimicrobial treatment

VII.21. A 30-year-old man with a history of hypertension presents to the emergency department with sudden onset of fever, chills, and right leg edema. On physical examination, temperature is 38.5°C, heart rate is 110 beats per minute, blood pressure is 130/80 mm Hg, respiratory rate is 20 breaths per minute, and body mass index is 40. His right leg is edematous with erythema involving the entire right leg from the ankle to the upper third of the leg. The leg is warm and tender. No fluctuance or drainage is noted. On his right foot, the interdigital skin between the third and fourth toes is macerated and erythematous. Laboratory results include a white blood cell count of 12×10^9/L with 80% polymorphonuclear cells. Which of the following is the most appropriate next step?

a. Vancomycin therapy
b. Right leg computed tomography with intravenous contrast agent
c. Cefazolin therapy
d. Imipenem therapy

VII.22. A 23-year-old man presents with right wrist and ankle pain. For about 3 days, he has been having fever, chills, and swelling of the right wrist and right ankle. On physical examination, he has a scatter pustular and petechial rash involving the hands and feet. Edema and pain are present on active and passive range of motion of the right wrist and right ankle. The result of arthrocentesis of the right ankle is cloudy fluid with 55,000/μL total nucleated cells with 90% polymorphonuclear cells. Gram stain is negative, and there are no crystals. He denies any urethral discharge or dysuria. He was tested for HIV and other sexually transmitted infections 6 months ago. He denies any recreational drug use. He works as a bartender and recently started a relationship with a male partner. Synovial fluid culture is growing gram-negative cocci. Which of the following is the most likely organism causing this infection?

a. *Kingella kingae*
b. *Staphylococcus aureus*
c. *Klebsiella pneumoniae*
d. *Neisseria gonorrhoeae*

VII.23. A 35-year-old woman who works as a kindergarten teacher presents with hand and knee pain. About 4 days ago, she had development of fever followed by a faint erythematous, macular rash involving the trunk and limbs. Two days later, pain and swelling of the right knee and proximal interphalangeal and metacarpophalangeal joints on both hands developed. On physical examination, temperature is 37.1°C, heart rate is 60 beats per minute, blood pressure is 120/80 mm Hg, and respiratory rate is 16 breaths per minute. Multiple joints of both hands and the right knee are swollen and warm. An aspiration of the right knee shows clear synovial fluid with 20,000/μL total nucleated cells, 45% neutrophils, and 55% lymphocytes. Gram stain result was negative. No crystals were seen. She received all the scheduled childhood vaccines. Several children in her classroom recently had diffuse rash that also involved the cheeks. Which of the following is the most appropriate next step?

a. Vancomycin therapy
b. Parvovirus B19 antibody test for immunoglobulins M and G
c. Colchicine for treatment of crystal arthropathy
d. Rheumatoid factor test

Answers[1]

VII.1. **Answer c.**

This patient presents with clinical findings suspicious for bacterial meningitis. A microbiologic cause is established with blood cultures and cerebrospinal fluid analysis with Gram stain and culture, followed by an empirical antimicrobial regimen. Empirical coverage should include standard activity against *Neisseria meningitidis* and *Streptococcus pneumoniae* (with combination of vancomycin and ceftriaxone), in addition to expanded coverage with ampicillin for *Listeria monocytogenes* given his age (>50 years). Dexamethasone is recommended for all adults before or together with the first dose of empirical antimicrobials given improved outcomes in cases of *Streptococcal pneumoniae* meningitis. CT of the head is not recommended before diagnostic LP because the patient has no notable contraindications to LP (including lack of immunocompromised history, no history of central nervous system disease, no reported seizure, no papilledema, no altered consciousness, and no focal neurologic deficits). The patient has not reported recent neurosurgical procedures or trauma, and empirical *Pseudomonas* coverage is not necessary for community-onset meningitis.

VII.2. **Answer b.**

The patient presents with new reported back pain within 1 week of a documented bloodstream infection due to MSSA. New-onset back pain in the setting of a recent bloodstream infection should always trigger a concern for development of spinal diskitis or osteomyelitis, and, in the setting of associated neurologic deficits, such as weakness or numbness, epidural abscess must be ruled out. The best test in this case is MRI of the spine to confirm the clinical suspicion, followed by evaluation by the neurosurgical service for potential surgical options in the setting of detectable neurologic symptoms. Given the recent documented bloodstream infection, the most likely causative pathogen responsible for the back pain is MSSA, and the addition of vancomycin is not necessary. The patient's immunosuppressive therapy should be withheld because she is receiving treatment for the life-threatening infection. A repeat TEE could be considered if other manifestations of new embolic phenomenon are suspected, but it would not be necessary because the patient recently had TEE and her symptoms likely started at the time of the original MSSA bloodstream infection.

VII.3. **Answer a.**

This patient's frontal lobe abscess is likely the result of direct spread of infection from bacterial sinusitis. As such, empirical therapy should be directed at the organisms that are most likely the cause of sinusitis. The most common organisms in this scenario include those of *Streptococcus* species, *Haemophilus* species, and anaerobes such as *Bacteroides* and *Fusobacterium. E coli* infection is not a common cause of community-onset brain abscess and, like *Pseudomonas* infection, typically follows neurosurgical procedures. *Pseudomonas* infection, however, should also be considered with an otogenic source of brain abscess. *C albicans* infection should be suspected in immunocompromised patients and intravenous drug users and is usually part of hematogenous spread.

VII.4. **Answer d.**

Depending on the wife's sexual activity with her husband and potentially other risks for HIV, she may be an appropriate candidate for PrEP. Before PrEP is recommended, she needs to be evaluated, including confirmation of her HIV-negative status and the status of her kidney function. PrEP is indicated for all persons who are not infected with HIV but are at high risk for HIV infection. A formulation of tenofovir and emtricitabine is the only product that has current approval for PrEP.

VII.5. **Answer c.**

The patient has a mononucleosis-like syndrome; the differential diagnosis for this includes acute retroviral syndrome, primary Epstein-Barr virus infection, and primary cytomegalovirus infection. However, given the temporal association of this illness with high-risk behavior for HIV, testing for HIV becomes the most important next step in evaluating this patient. The Centers for Disease Control and Prevention recommends the antigen-antibody combination assay as the first step in the HIV testing algorithm. The interval between the possible exposure and testing in this patient is within the time frame appropriate for using this assay, which usually is able to detect HIV infection by 15 days after infection. Preexposure prophylaxis should not be initiated before ensuring the patient is not infected with HIV. HIV-1 nucleic acid testing is recommended for specimens that have a negative or indeterminate result and HIV is highly suspected.

VII.6. **Answer d.**

Antiretroviral therapy is indicated for all patients with HIV regardless of the CD4 cell count or HIV RNA level. Primary prophylaxis against *Pneumocystis* pneumonia is recommended when the CD4 cell count is less than 200/mcL.

VII.7. **Answer c.**

The patient presented with febrile neutropenia complicated by hemodynamic instability. Although vancomycin should not be used as a routine part of empirical coverage for neutropenic fever, in certain clinical scenarios, including the presence of hemodynamic instability, empirical use of vancomycin is recommended. Broadening antifungal coverage could be considered in patients with persistent or recurrent fever after 4 to 7 days of empirical antibacterial therapy.

VII.8. **Answer b.**

Rituximab is associated with hepatitis B reactivation, including in patients who were negative for hepatitis B surface antigen and positive for hepatitis B core antibody before treatment. Therefore, if rituximab therapy is planned, patients should have a hepatitis B core antibody test done as part of the pretreatment evaluation. Hepatitis B reactivation may present with hepatitis flare, but it also can lead to fulminant hepatitis. Although hepatitis C infection is possible, this would be a newly acquired infection given the recent negative screening result, and presentation with fulminant hepatitis is less likely. Tuberculosis as a cause of the patient's fulminant hepatitis is less likely given the lack of epidemiologic clues or other signs or symptoms, although tuberculosis reactivation has been reported with use of rituximab. Hepatitis A can present as fulminant hepatitis; however, the patient had evidence of previous vaccination that should confer lifelong protection from reinfection.

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[1] Mayo Clinic does not endorse products mentioned in this section.

VII.9. Answer a.

The patient is a recent transplant recipient. His pretransplant serologic results indicate that he is a mismatch for CMV, and he is thus in the highest-risk category for development of primary CMV disease after transplant. His evaluation thus far, including *C difficile* testing and gastrointestinal polymerase chain reaction testing, has eliminated bacterial and routine viral causes of diarrhea. Therefore, the best next step is further evaluation of potential CMV disease presenting as CMV colitis. CMV colitis is the most common end-organ disease presentation in the solid transplant population. Testing would include CMV viral load in the blood (not an answer choice) and endoscopy with biopsy because histopathologic analysis can show classic owl's eye inclusions, and specific immunochemistry staining for CMV can confirm the diagnosis. Endoscopy is recommended because CMV can occur with a negative result of CMV viral load testing in the serum. Serologic tests for CMV are useful before transplant to identify the risk of infection after transplant. However, they are not useful during acute evaluation of viral illness after transplant. Although the patient is noted to be a mismatch for EBV, this status increases his risk for posttransplant lymphoproliferative disorder, the diagnosis of which would still require a tissue biopsy. Because the patient has already had a multiplex gastrointestinal polymerase chain reaction panel, routine blood cultures are not likely to detect a bacterial cause of the prolonged nonbloody diarrhea.

VII.10. Answer a.

Because the patient has localized rather than disseminated zoster and his lesions are crusted over, he is no longer considered contagious and is able to return to work. If he were to return to work before the lesions crusted over, he should keep them covered, because localized zoster transmission can occur through direct contact. No respiratory precautions are recommended in cases of localized zoster. People with zoster can spread varicella-zoster virus only to people who have not had previous varicella infection or vaccine.

VII.11. Answer c.

Despite the patient's lack of known tick exposures, in an endemic Lyme disease area his rash is most concerning for erythema migrans (EM), consistent with the lack of response to cellulitis treatment. He should be empirically managed with doxycycline for EM. Because EM occurs early in Lyme disease, serologic testing for Lyme disease is not recommended because seroconversion has not occurred at the time of clinical presentation. His history is not consistent with purulent cellulitis, and methicillin-resistant *Staphylococcus aureus* coverage is not indicated with trimethoprim-sulfamethoxazole.

VII.12. Answer c.

The patient presents with severe symptoms after a clinical suspicion of mononucleosis syndrome. The severity of her presentation, the severe cytopenias, thrombocytopenia, high ferritin level, and increased triglyceride level are clues for possible hemophagocytic lymphohistiocytosis (HLH). A bone marrow biopsy is critical for establishing the diagnosis early. Ebstein-Barr virus is one of the commonly identified infectious triggers of HLH. Excisional lymph node biopsy is not the appropriate next step given the clinical suspicion of HLH. Splenic rupture may occur in the setting of splenomegaly after mononucleosis. However, this would not be suspected with normal findings on abdominal examination and normal computed tomography findings.

VII.13. Answer b.

A negative result of TEE does not rule out infective endocarditis. Often, the initial TEE was performed too early. If clinical suspicion of infective endocarditis remains, repeating TEE in 3 to 5 days is recommended (or sooner if clinical findings change). During this interval, vegetations may reach a detectable size or abscess cavities or fistulous tracts may become evident. PET with CT imaging has been shown to be helpful for the diagnosis of infective endocarditis, especially in the presence of prosthetic valves when TEE is inconclusive. Cardiac MRI has also been helpful when TEE is inconclusive. Both PET with CT and cardiac MRI may be considered after repeat TEE if clinical suspicion remains high. TTE is not helpful because its diagnostic sensitivity is approximately 50%.

VII.14. Answer c.

The 2007 American Heart Association guidelines for prevention of infective endocarditis drastically reduced the number of indications for antibiotic prophylaxis before invasive procedures. Antibiotics are no longer recommended for patients with moderate-risk cardiac conditions (ie, mitral valve prolapse, atrial septal defect, ventricular septal defect, hypertrophic cardiomyopathy), which this patient has. Antibiotics are needed only for patients with high-risk cardiac conditions: prior infective endocarditis, prosthetic heart valves, cardiac transplant recipients with valvulopathy, and certain congenital heart diseases (unrepaired cyanotic congenital heart disease including palliative shunts and conduits, repair with prosthetic material or device within the past 6 months, or residual defects at the site of a prosthetic patch or device). Furthermore, antibiotics are no longer recommended before gastrointestinal, genitourinary, or respiratory procedures. For patients with high-risk cardiac conditions, antibiotic prophylaxis is reasonable before all dental procedures that involve manipulation of gingival tissues or the periapical region of teeth or perforation of oral mucosa.

VII.15. Answer c.

This patient has hospital-acquired pneumonia (HAP). The 2016 guidelines of the Infectious Diseases Society of America recommend empirical antibiotic treatment of HAP and ventilator-acquired pneumonia based on the patient's risk of mortality and risk of having a multidrug-resistant organism such as MRSA, *Pseudomonas aeruginosa*, and other gram-negative bacilli. The guidelines for HAP are as follows:

1. If there are no high-risk factors for mortality (need for ventilator support because of pneumonia and septic shock), no IV antibiotic treatment in the past 90

days, and the treatment unit's prevalence of MRSA is more than 20% or not known, then only 1 antibiotic with both methicillin-sensitive *Staphylococcus aureus* and antipseudomonal coverage is needed: cefepime, piperacillin-tazobactam, levofloxacin, imipenem, or meropenem.

2. If there are no high-risk factors for mortality but increased risk factors for MRSA, then IV vancomycin should be added to the above regimen.
3. If there are high-risk factors for mortality or IV antibiotic treatment in the past 90 days, then vancomycin and 2 antipseudomonal agents should be provided empirically.

VII.16. Answer c.

Because the patient is older than 65 years and has a respiratory rate more than 30 breaths per minute and a serum urea nitrogen value more than 19 mg/dL, she has 3 points on the CURB-65 index (*c*onfusion, *u*remia [serum urea nitrogen >19 mg/dL], *r*espiratory rate [>30 breaths per minute], *b*lood pressure [systolic <90 mm Hg or diastolic ≤60 mm Hg]). This score suggests that her community-acquired pneumonia should be treated in the inpatient setting, although it likely is not severe enough to require admission to an intensive care unit. Empirical antimicrobial therapy should cover routine community-acquired pneumonia organisms, including *Streptococcus pneumoniae*, and atypical organisms, such as *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*, among others. The Infectious Diseases Society of America recommends treatment with either a fluoroquinolone with strong activity against *S pneumoniae* (ie, levofloxacin or moxifloxacin but not ciprofloxacin) or a β-lactam antimicrobial in combination with either a macrolide or doxycycline.

VII.17. Answer a.

The cutoffs for millimeters of induration used for tuberculin skin tests are based on the pretest probability of latent tuberculosis infection and the potential consequences if it is untreated (eg, tuberculous meningitis in a child). The highest-risk patients, for which a cutoff of 5 mm or more would be used, include those with strong clinical or radiographic evidence of exposure to tuberculosis or those with severe reduction in cellular immunity. Patients receiving tumor necrosis factor-α inhibitors, such as infliximab for rheumatoid arthritis, are considered in this highest-risk stratification. The other patients listed are considered in the intermediate-risk stratification.

VII.18. Answer b.

Lung abscess and empyema are infrequent, but important, consequences of pneumonia. The patient likely has an aspiration pneumonitis complicated by lung abscess and empyema given the history of alcohol use disorder and the radiographic evidence of right lower lobe involvement. Although there are many bacterial causes of this syndrome, it is most commonly caused by *Klebsiella pneumoniae*.

VII.19. Answer d.

The patient is presenting with acute uncomplicated cystitis. She has no signs or symptoms suggestive of pyelonephritis. The first-line empirical antimicrobial recommendations for acute uncomplicated cystitis include nitrofurantoin 100 mg orally twice a day for 5 days, fosfomycin 3 g sachet for 1 dose, and trimethoprim-sulfamethoxazole (if local resistance patterns are <20%). Ciprofloxacin is not correct because resistance to the fluoroquinolones is increasing among urinary bacterial pathogens, and the patient does not need therapy for 7 days. Clindamycin is incorrect because it covers only gram-positive pathogens, and most urinary tract infections are caused by the gram-negative *Enterobacteriaciae.* Amoxicillin is incorrect because many gram-negative bacterial pathogens will have resistance to it.

VII.20. Answer d.

This patient has asymptomatic bacteriuria. She has no urinary symptoms suggestive of infection. She does not need treatment. The only patients with asymptomatic bacteriuria who should undergo treatment are pregnant women, patients undergoing urologic surgery, and renal transplant recipients (within 3 months from time of transplant).

VII.21. Answer c.

This patient is presenting with nonpurulent cellulitis involving a lower extremity. Nonpurulent cellulitis is most commonly due to β-hemolytic streptococci or methicillin-susceptible *Staphylococcus aureus*. A first-generation oral or parenteral cephalosporin (ie, cephalexin, cefadroxil, or cefazolin) is the usual initial choice when methicillin-resistant *S aureus* is not suspected. Because there is no purulence or drainage and there are no risk factors for methicillin-resistant *S aureus*, treatment with vancomycin is not required. Imipenem has activity against β-hemolytic streptococci and methicillin-susceptible *S aureus*, but it has a broader spectrum of activity than first-generation cephalosporins, which are not required here. In this patient, there are no concerns for deeper infection at this time; therefore, computed tomography of the extremity is not indicated.

VII.22. Answer d.

Neisseria gonorrhoeae is a gram-negative diplococcus that is sexually transmitted and can cause a disseminated infection presenting with rash, tenosynovitis, or septic arthritis. It is the most common cause of septic arthritis in young and sexually active persons. *Kingella kingae* is a gram-negative coccobacillus that causes septic arthritis mainly in children. This patient's age and social history are more suggestive of *N gonorrhoeae* disseminated disease. *Staphylococcus aureus* is the most common cause of septic arthritis in adults and causes monoarticular septic arthritis in 80% to 90% of cases. On synovial fluid analysis, *S aureus* appears as gram-positive cocci. Gram-negative bacilli such as *K pnuemoniae* can cause septic arthritis, but mainly in elderly persons, intravenous drug users, or immunosuppressed patients.

VII.23. Answer b.

This patient most likely has a parvovirus infection with polyarthritis. Parvovirus B19 causes a rash illness in children that is transmitted from person to person by contact with respiratory secretions. Susceptible adults usually contract the infection after exposure to school-aged children attending schools or daycare centers. Adults may present with a febrile illness with or without rash followed by polyarthropathy or polyarthritis. This presentation is not consistent with bacterial septic arthritis based on the presence of rash and polyarticular involvement. Colchicine is indicated in crystal-induced arthritis such as gout. Because synovial fluid analysis showed no crystals, therapy with colchicine is not indicated. Although patients with parvovirus infections can present with polyarthropathy similar to rheumatoid arthritis, acute onset of fever and rash after recent exposure to children with rash illness is more consistent with an infectious process such as parvovirus.

Section

VIII

Nephrology

51

Acid-Base Disorders

QI QIAN, MD

Determination of Acid-Base Status

Simple acid-base disorders are defined by changes in pH and the initial change in 1 of 2 variables: serum bicarbonate (HCO_3^-) concentration and partial pressure of CO_2 (Pco_2). Low pH indicates acidosis, and high pH indicates alkalosis. If 1 of the 2 variables (HCO_3^- or Pco_2) decreases (or increases), the other also decreases (or increases)—a compensatory change that minimizes the change in the ratio and the pH—as shown in the Henderson-Hasselbalch equation. Emphasis has been placed on the Henderson-Hasselbalch equation because it describes the 4 acid-base disorders and their compensatory changes (Figure 51.1).

The reference range for serum $[HCO_3^-]$ is 22 to 29 mmol/L. The adequacy of the compensation can be evaluated by using the Winter formula for patients who have metabolic acidosis (serum $[HCO_3^-]$ <24 mmol/L) and by using the Rule of 15 for patients with serum $[HCO_3^-]$ of 10 to 40 mmol/L.

$$\text{Winter formula: Expected } Pco_2 = (1.5 \times \text{serum}[HCO_3^-]) + 8(-2)$$

$$\text{Rule of 15: Expected } Pco_2 = [HCO_3^-] + 15$$

An example of acid-base evaluation in the clinical setting is shown in Box 51.1.

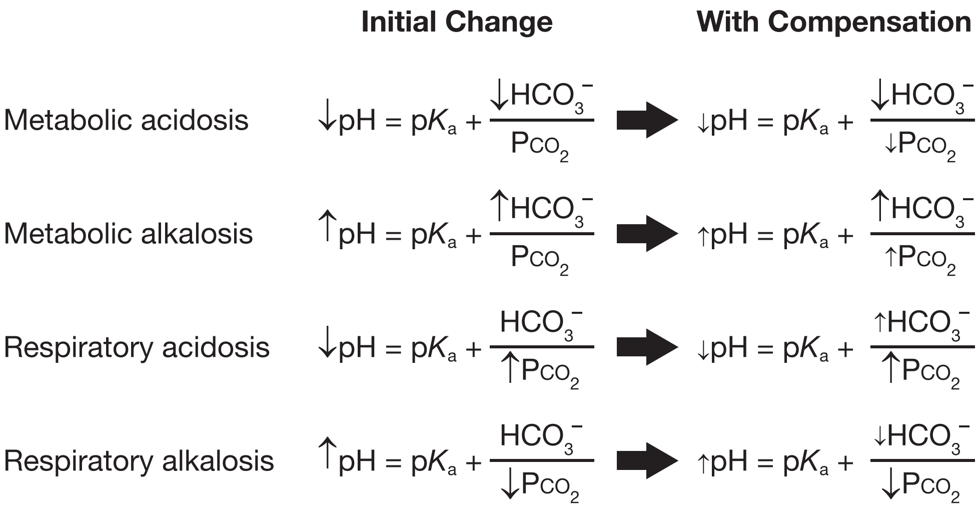
Initial Change
With Compensation
Metabolic acidosis
$\downarrow pH = pK_a + \frac{\downarrow HCO_3^-}{Pco_2}$
$\downarrow pH = pK_a + \frac{\downarrow HCO_3^-}{\downarrow Pco_2}$
Metabolic alkalosis
$\uparrow pH = pK_a + \frac{\uparrow HCO_3^-}{Pco_2}$
$\uparrow pH = pK_a + \frac{\uparrow HCO_3^-}{\uparrow Pco_2}$
Respiratory acidosis
$\downarrow pH = pK_a + \frac{HCO_3^-}{\uparrow Pco_2}$
$\downarrow pH = pK_a + \frac{\uparrow HCO_3^-}{\uparrow Pco_2}$
Respiratory alkalosis
$\uparrow pH = pK_a + \frac{HCO_3^-}{\downarrow Pco_2}$
$\uparrow pH = pK_a + \frac{\downarrow HCO_3^-}{\downarrow Pco_2}$

Figure 51.1. *Four Types of Simple Acid-Base Disorders. The initial insult of acid or base influx causes large changes in pH and in 1 of the 2 components of the Henderson-Hasselbalch equation (bicarbonate $[HCO_3^-]$ or Pco_2). With compensation, the other component changes accordingly to minimize the net change in the ratio and blood pH. The arrow size indicates the relative amount of increase (↑) or decrease (↓). pK_a indicates the negative logarithm of the acid dissociation constant.*

Box 51.1 • Example of Acid-Base Determination

Patient: A 37-year-old woman with a history of Sjögren syndrome and hypothyroidism was admitted for shortness of breath. Evaluation showed significant electrolyte and acid-base imbalance. Physical examination findings were unremarkable except for mild tachypnea. Laboratory test results included: $[Na^+]$, 134 mmol/L; $[K^+]$, 2.6 mmol/L; $[Cl^-]$, 115 mmol/L; $[HCO_3^-]$, 10 mmol/L; and [creatinine], 0.6 mg/dL. Arterial blood gas results were pH 7.25 and $P\text{CO}_2$, 25 mm Hg.

Question: What is the patient's acid-base status?

Answer: The first step is to look at the blood pH. The patient's blood pH is decreased, indicating acidemia. The next step is to identify which of the 2 variables ($P\text{CO}_2$ or HCO_3^-) is decreased, like the blood pH. Her serum $[HCO_3^-]$ is decreased along with the blood pH, indicating metabolic acidosis. The next step is to determine whether the patient has an appropriate degree of compensation, which indicates a singular metabolic acidosis without another primary abnormality. If the compensation is much more or much less than expected, there is most likely a second, primary respiratory abnormality. For example, if the $P\text{CO}_2$ is lower than the expected compensation, a primary respiratory alkalosis is present in addition to a primary metabolic acidosis; a $P\text{CO}_2$ higher than expected indicates the existence of an additional primary respiratory acidosis.

One of 2 methods is used to determine the expected respiratory compensation ($P\text{CO}_2$):

1. Winter formula: Expected $P\text{CO}_2 = (1.5\times[HCO_3^-]) + 8$ (±2). For this patient, expected $P\text{CO}_2 = 23\pm2$ mm Hg. This formula is used if the patient's serum $[HCO_3^-]$ is in the acidemic range (<24 mmol/L).
2. Rule of 15: Expected $P\text{CO}_2 = [HCO_3^-]+15$. The value (25 for this patient) should equal the last 2 digits of the pH if the patient has a single acidosis with adequate respiratory compensation. The Rule of 15 is relatively simple and applicable if the $[HCO_3^-]$ is between 10 and 40 mmol/L.

On the basis of this calculation, the patient has a normal anion gap metabolic acidosis with appropriate compensation.

Metabolic Acid-Base Disorders

Metabolic Acidosis

Metabolic acidosis is characterized by a decrease in pH, a decrease in serum $[HCO_3^-]$, and a compensatory decrease in $P\text{CO}_2$. Metabolic acidosis can be categorized as normal anion gap (AG) acidosis or high AG acidosis.

The AG is the difference between the serum sodium concentration and the sum of the chloride and HCO_3^- concentrations.

$$AG = \left[Na^+\right] - \left(\left[Cl^-\right] + \left[HCO_3^-\right]\right)$$

The AG should be in the range of 8 to 12 mmol/L (mEq/L).

Normal AG Acidosis

Normal AG acidosis can occur as a result of 1) HCO_3^- (or HCO_3^- equivalent) loss from the kidney or gastrointestinal tract, 2) defects in kidney acid excretion, or 3) infusion of fluids with a high $[Cl^-]$ (eg, intravenous, large-volume [>2 L] infusion of 0.9% saline).

Common causes of normal AG acidosis are listed in Box 51.2.

Box 51.2 • Common Causes of Metabolic Acidosis and Metabolic Alkalosis

- Metabolic acidosis
  - Normal anion gap acidosis
    - Renal tubular acidosis
    - Diarrhea
    - Stage 2 or 3 chronic kidney disease
    - Ureterosigmoid fistula
    - Drugs such as carbonic anhydrase inhibitors (eg, acetazolamide)
  - High anion gap acidosis[a]
    - Glycols (ethylene and propylene)
    - Oxoproline
    - L-Lactate
    - D-Lactate
    - Methanol
    - Aspirin
    - Renal failure
    - Ketones
- Metabolic alkalosis
  - Chloride-responsive alkalosis
    - Volume contraction
    - Diuretics
    - Vomiting
    - Gastric suction
  - Chloride-resistant alkalosis
    - Hyperaldosteronism
    - Corticosteroids
    - Renal artery stenosis
    - Bartter syndrome
    - Gitelman syndrome
    - Severe hypokalemia
    - Milk-alkali syndrome

[a] *GOLDMARK* is the mnemonic for the major causes of high anion gap acidosis.

Table 51.1 • Features of 3 Types of Renal Tubular Acidosis

Feature	Type 1: Distal Tubular	Type 2: Proximal Tubular	Type 4: Hyporeninemic Hypoaldosteronism
Defect	H$^+$ excretion in distal tubule	HCO$_3^-$ reabsorption in proximal tubule	Low renin, low aldosterone
Cause and clinical setting	Acquired: Connective tissue diseases, interstitial renal diseases Drugs: Amphotericin B Hereditary: rare	Acquired: dysproteinemia (MM), interstitial renal diseases (less frequently), lead or mercury toxicity Drugs: • CA inhibitors (topiramate, acetazolamide) • Ifosfamide • Antiretroviral agents (tenofovir) • Valproic acid • Expired tetracycline Hereditary: glycogen storage disease, hereditary fructose intolerance, mitochondrial diseases, cystinosis, Wilson disease	DM, mild-moderate CKD Drugs: • ACEI/ARBs • Renin inhibitors • Aldosterone antagonists • K$^+$-sparing diuretics • Calcineurin inhibitors • NSAIDs • Heparin infusion
Serum [K$^+$]	Low	Low	High
Urine pH	Always high (>5.3)	Low (when [HCO$_3^-$] <Tm)	Variable
Urinary loss of glucose, amino acids, and phosphate (Fanconi syndrome)	No	Yes	No
Nephrocalcinosis or nephrolithiasis	Yes	No	No
Acidemia	Severe if no treatment	Self-limited	Mild
Alkali treatment	Small requirement	Large requirement; treat the cause	Small requirement
FE-HCO$_3^-$	<5%	Can be high with alkali treatment	Variable

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CA, carbonic anhydrase; CKD, chronic kidney disease; DM, diabetes mellitus; FE-HCO$_3^-$, fractional excretion of bicarbonate; MM, multiple myeloma; NSAID, nonsteroidal anti-inflammatory drug; Tm, tubular transport maximum.

Modified from Dhondup T, Qian Q. Acid-base and electrolyte disorders in patients with and without chronic kidney disease: an update. Kidney Dis (Basel). 2017 Dec;3(4):136-48; used with permission.

Renal tubular acidosis is one type of normal AG acidosis. There are 3 main types of renal tubular acidosis, which are summarized and compared in Table 51.1:

1. Type 1—distal tubular acidosis due to defects in hydrogen ion excretion in the collecting duct
2. Type 2—proximal tubular acidosis due to defects in proximal tubular HCO$_3^-$ reclamation
3. Type 4—hyporeninemic hypoaldosteronism

High AG Acidosis

High AG acidosis is characterized by a decrease in blood pH, a decrease in serum [HCO$_3^-$], and an AG greater than 12 mmol/L. Regardless of the blood pH, the AG should always be calculated, because with concurrent acid-base alterations, a high AG acidosis may not be apparent.

In patients with an abnormal serum albumin level, AG should be corrected for alterations in serum albumin. For every 1 g/dL decrease in serum albumin, the expected AG should decrease accordingly by 2.5 mmol/L (eg, if albumin decreases from 4.5 to 3.5 g/dL, the expected AG should decrease from 10 to 7.5 mmol/L). Cationic paraproteins, polyclonal gammopathy, hypercalcemia, lithium and bromide, or iodide intoxication may lower AG to less than 8 mmol/L, whereas hemoconcentration, metabolic alkalosis, severe hyperphosphatemia, and anionic paraproteins may slightly increase (by <3 mmol/L) the calculated AG.

KEY FACTS

✓ Use the Winter formula to determine the expected respiratory compensation in metabolic acidosis (serum [HCO$_3^-$] <24 mmol/L)

✓ Use the Rule of 15 to determine the expected respiratory compensation when [HCO$_3^-$] is 10-40 mmol/L

✓ Acid-base problems—calculate the AG regardless of the blood pH

✓ Correct the AG for low serum albumin value

In recent years, several new anion-generating acids have been recognized as causes of high AG acidosis. A mnemonic for the major causes of high AG acidosis is **GOLDMARK** (Box 51.2). Causes and features of high AG acidosis are shown in Table 51.2.

Key Definition

GOLDMARK: *mnemonic for major causes of AG metabolic acidosis (**g**lycols [ethylene and propylene], **o**xoproline, **L**-lactate, **D**-lactate, **m**ethanol, **a**spirin, **r**enal failure, and **k**etones).*

Diagnosis and Therapy

In most cases, the clinical scenario indicates the cause of acidosis. Among the causes of high AG acidosis, L-lactic acidosis is common, especially in critically ill patients. L-Lactic acidosis can be subdivided into 2 types, A and B. Type A lactic acidosis develops with tissue hypoxia, as in shock, severe anemia, and hypoxia from pulmonary diseases. Type B lactic acidosis develops in conditions of mitochondrial oxidative impairment, including MELAS syndrome (*m*itochondrial *e*ncephalomyopathy, *l*actic *a*cidosis, and *s*trokelike episodes), cyanide intoxication, and use of certain medications (eg, metformin, linezolid, and reverse transcriptase inhibitors).

D-Lactic acidosis occurs mainly in patients with short gut syndrome and overgrowth of gut bacteria. The bacteria generate D-lactate, which causes high AG acidosis. Notably, most clinical laboratories test for L-lactate but not D-lactate unless requested. Therefore, if D-lactic acidosis is suspected, measurement of D-lactate must be requested specifically.

If toxic alcohol ingestion is suspected, the osmolal gap should be calculated in addition to the AG. The toxic alcohols (especially methanol and ethylene glycol) are osmotically active molecules. Methanol is metabolized to formic acid, which causes blindness. Ethylene glycol is metabolized to glycolic acid and oxalic acid, which leads to the formation of oxalate crystals that may be visualized in urine. Before their conversion to toxic acids, the alcohols generate an osmolal gap (ie, the measured serum osmolality exceeds the calculated serum osmolality by >10 mOsm/kg).

$$\begin{aligned}\text{Calculated Serum Osmolality} = {} & 2\times([\text{Sodium}]+[\text{Potassium}]) \\ & +(\text{Blood Urea Nitrogen}/2.8) \\ & +([\text{Glucose}]/18)\end{aligned}$$

If the osmolal gap is increased, treatment should be instituted immediately to block the toxic alcohols (parent compounds) from being metabolized. Inhibitors of alcohol dehydrogenase, such as fomepizole (4-methylpyrazole), effectively block toxic alcohol metabolism. In severe cases, hemodialysis is necessary.

Aspirin (salicylate) intoxication in adults typically causes high AG acidosis and simultaneous respiratory alkalosis, but it does not cause an osmolal gap.

Metabolic Alkalosis

Definition

Metabolic alkalosis is characterized by an increase in pH, an increase in [HCO_3^-], and a compensatory increase in $P\text{CO}_2$. Metabolic alkalosis can result from a net loss of acid or a net gain of HCO_3^-. Clinical manifestations include weakness, muscle cramps, hyperreflexia, alveolar hypoventilation, and arrhythmias. Common causes of metabolic alkalosis are listed in Box 51.2. The major causes, pathophysiology, diagnostic features, and therapy are summarized in Table 51.3.

Diagnosis and Therapy

Metabolic alkalosis associated with hypovolemia is characterized by a low urine chloride concentration (<20 mmol/L) and is responsive to volume expansion with isotonic saline infusion or oral salt tablets (ie, chloride-responsive alkalosis) (Box 51.2). Metabolic alkalosis associated with primary mineralocorticoid excess is usually characterized by hypertension and hypervolemia, a high urine chloride concentration (≥20 mmol/L), and resistance to saline (ie, chloride-resistant alkalosis), but it is responsive to mineralocorticoid antagonizers (eg, spironolactone). Acetazolamide can potentially be used after serum potassium is repleted because alkalosis and acetazolamide can cause kaliuresis.

Respiratory Acid-Base Alterations

Respiratory acidosis is characterized by a decreased pH, an increased $P\text{CO}_2$, and a compensatory increase in serum [HCO_3^-].

Respiratory alkalosis is characterized by an increased pH, a decreased $P\text{CO}_2$, and a compensatory decrease in serum [HCO_3^-].

Respiratory acidosis and respiratory alkalosis can be caused by defects in the central nervous system respiratory center, the chest wall (ribs, nerves, and muscles), and the lung parenchyma. Causes of and expected metabolic compensations for acute and chronic respiratory acid-base alterations are summarized in Box 51.3. Therapy for respiratory acid-base alterations is directed at the specific causes.

KEY FACTS

- ✓ Lactic acidosis—rule out medications as the cause
- ✓ For patients with acid-base disorder and decreased mental status (eg, toxic alcohol ingestion), calculate both the osmolal gap and the AG
- ✓ Aspirin (salicylate) intoxication in adults—characterized by high AG acidosis and respiratory alkalosis

Table 51.2 • Features of High AG Acidosis (GOLDMARK)

Type of Acidosis	Cause	Pathophysiology	Clinical Features	Laboratory Features	Treatment
Ethylene **g**lycol	Antifreeze poisoning	Ethylene glycol ↓ [Glycoaldehyde] ↓ [Glycolate] ↓ [Glyoxylate] ↓ [Oxalate crystals]	Flank pain, hematuria, renal failure, death	Serum OG >10[a] Urine CaOx crystals AKI	Fomepizole/ethanol Dialysis (if severe acidosis and/or AKI are present)
Propylene **g**lycol	Prolonged IV infusion of benzodiazepine/ phenobarbital	Propylene glycol is metabolized to lactic acid	Dysrhythmias Hypotension Seizure Coma	Serum OG >10 ↑ [Lactate] AKI	Stop offending agent Fomepizole Dialysis (if severe acidosis and/or AKI are present)
Oxoproline	Chronic acetaminophen use in malnourished females	Glutathione stores can be exhausted by chronic use of acetaminophen, leading to accumulation of oxoproline	Nonspecific	↑ Urine and serum [5-oxoproline]	Stop acetaminophen Administer bicarbonate N-acetyl cysteine to replenish glutathione stores
L-Lactic acidosis	Type A: septic, cardiogenic or hypovolemic shock	Type A: develops owing to tissue hypoxia	Depends on the cause	↑ [Lactate]	Treat underlying cause Administer IV bicarbonate if pH <7.15
	Type B: MELAS, cyanide intoxication, severe inflammation Drugs (such as metformin, linezolid, reverse transcriptase), cancer	Type B: develops owing to mitochondrial impairment (except for cancer)			
D-Lactic acidosis	Short gut syndrome, gut bacterial overgrowth	Bacteria generate D-lactate, which causes acidosis	Abdominal discomfort Steatorrhea	↑ [D-Lactate] (must be specifically requested, if suspected)	Avoid large carbohydrate meals Bicarbonate Oral antibiotics
Methanol	Adulterated alcohol (moonshine) Accidental poisoning	↓ [Methanol] ↓ [Formaldehyde] Formic acid	Headache Visual loss Coma Death	Serum OG >10	Fomepizole/ethanol Dialysis (if severe acidosis and/or AKI are present)
Aspirin	Accidental or intentional overdose	Accumulation of salicylic acid + lactic acid Stimulation of CNS respiratory centers, causing primary respiratory alkalosis	Tinnitus Vertigo Nausea Vomiting	↑ Serum [salicylate] Mixed high AG acidosis and respiratory alkalosis (pH may not alter markedly)	Urine alkalinization Dialysis (if renal failure is present)
Renal failure	In advanced stages of CKD	↓ Acid excretion	Symptoms of uremia	↑ BUN ↑ [Cr]	Bicarbonate Dialysis
Ketoacidosis	In uncontrolled diabetes mellitus (usually type 1) Starvation	Insulin deficiency	Nausea/vomiting Abdominal pain ↓ Mentation Fruity breath Kussmaul respiration	↑ Serum [β-hydroxybutyrate] and [acetoacetate] ↑ [Glucose] + Urine ketones	Insulin IV fluids

Abbreviations: ↓, decreased; ↑, increased; AG, anion gap; AKI, acute kidney injury; BUN, blood urea nitrogen; CaOx, calcium oxalate; CKD, chronic kidney disease; CNS, central nervous system; Cr, creatinine; IV, intravenous; OG, serum osmolar gap.

[a] OG >10 is considered to be increased. OG = calculated serum osmolality – measured serum osmolality.

Calculated serum osmolality =2×([Na$^+$]+[K$^+$]) + ([Glucose]/18) + (BUN/2.8).

Isopropyl alcohol causes increased OG but does not cause high AG acidosis because it is metabolized to acetone.

Modified from Dhondup T, Qian Q. Acid-base and electrolyte disorders in patients with and without chronic kidney disease: an update. Kidney Dis (Basel). 2017 Dec;3(4):136-48; used with permission.

Table 51.3 • Features of Metabolic Alkalosis

Cause	Pathophysiology (Major)	Diagnostic Features in Addition to Metabolic Alkalosis	Therapy
Vomiting and gastric suction	Gastric acid loss Renal HCO_3^- absorption	↓ BP or normal BP Low urine $[Cl^-]$ (<20 mmol/L)	Normal saline
Hyperaldosteronism	↑ Renal H^+ excretion ↑ Proximal renal tubular HCO_3^- absorption	. . .	. . .
Primary hyperaldosteronism	. . .	↑ BP, high urine $[Cl^-]$ (≥ 20 mmol/L)	Correct the causes
Secondary hyperaldosteronism	. . .	. . .	Treat underlying cause
Renal artery stenosis		↑ BP, stenosis apparent with renal ultrasonography	
Volume depletion		↓ BP, low $[Cl^-]$ (<20 mmol/L)	
Diuretic use		↓ BP, high $[Cl^-]$ (≥ 20 mmol/L), hypokalemia	
Severe hypokalemia	↑ Renal H^+ excretion	Normal BP, polyuria	Potassium repletion
Exogenous alkali intake ($CaHCO_3$ and $NaHCO_3$)	Analogous to milk-alkali syndrome	Hypercalcemia, usually in patients with CKD	Discontinue alkaline intake
Posthypercapnic state	Net loss of carbonic acid	Mechanical ventilation in patients with severe COPD	↓ Ventilation
Liddle syndrome	Autosomal dominant inheritance Mutation in epithelial sodium channel present in collecting duct results in increased activity	↑ BP, hypokalemia, metabolic alkalosis	Potassium repletion and diuretics (amiloride preferred)
Glucocorticoid-remediable aldosteronism	Autosomal dominant inheritance Aldosterone synthesis is stimulated by corticotropin	↑ BP, hypokalemia ↑ Aldosterone ↓ Renin activity	Glucocorticoids
Apparent glucocorticoid excess	Defects in 11β-hydroxysteroid dehydrogenase Genetic defect (autosomal recessive inheritance), acquired (excessive licorice intake), or Cushing syndrome	↑ BP, hypokalemia ↓ Renin activity ↓ Aldosterone level ↑ Urine cortisol:cortisone ratio	Mineralocorticoid receptor blockade Symptomatic treatment
Bartter syndrome	Autosomal recessive inheritance with 5 types of genetic defects	Neonatal or childhood onset ↓ BP Hypokalemia Hypercalciuria High urine $[Cl^-]$ (≥ 20 mmol/L)	Sodium and potassium repletion
Gitelman syndrome	Autosomal recessive inheritance Mutations in distal sodium-Cl^- cotransporters	Adolescence or adulthood onset ↓ BP or normal BP Hypokalemia Hypocalciuria High urine $[Cl^-]$ (≥ 20 mmol/L)	Sodium and potassium repletion

Abbreviations: ↓, decreased; ↑, increased; BP, blood pressure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

Modified from Dhondup T, Qian Q. Acid-base and electrolyte disorders in patients with and without chronic kidney disease: an update. Kidney Dis (Basel). 2017 Dec;3(4):136-48; used with permission.

Box 51.3 • Respiratory Acid-Base Alterations

- Causes of respiratory acidosis
  - CNS respiratory depression
    - Injury: trauma, infarct, hemorrhage, tumor
    - Drugs: opiates, sedatives, anesthetics
    - Hypoventilation of obesity (eg, pickwickian syndrome)
    - Cerebral hypoxia
  - Nerve or muscle
    - Guillain-Barré syndrome, myasthenia gravis, various myopathies
    - Diaphragmatic factors: paralysis or splinting, muscle relaxants
    - Toxins (eg, organophosphates, snake venom)
  - Chest wall, airway, lung
    - Airway: upper and lower airway obstruction
    - Chest wall trauma: flail chest, contusion, hemothorax, pneumothorax
    - Lung: pulmonary edema, ARDS, aspiration
  - Carbon dioxide excess
    - Hypercatabolic states: malignant hyperthermia
    - Addition of CO_2 to inspired gas
    - Insufflation of CO_2 into body cavity (eg, for laparoscopic surgery)
- Causes of respiratory alkalosis
  - CNS respiratory stimulation
    - Pain, hyperventilation syndrome, anxiety, psychosis, infection, trauma, cerebrovascular accident
  - Hypoxia
    - High altitude, severe anemia, right-to-left shunts
  - Drugs
    - Progesterone, methylxanthines, salicylates, catecholamines, nicotine
  - Endocrine conditions
    - Progesterone (pregnancy)
  - Pulmonary conditions
    - Pneumonia, edema, embolism, asthma
  - Miscellaneous
    - Sepsis, hepatic failure, recovery phase of metabolic acidosis

Abbreviations: ARDS, acute respiratory distress syndrome; CNS, central nervous system.

Mixed Acid-Base Disorders

Definition

Mixed acid-base disorders are the presence of 2 primary acid-base disorders—specifically, one primary disorder with a compensation that is out of proportion to the expected estimation.

Acid-Base Analysis

There are 5 steps to analyzing acid-base status in a patient.

Step 1: *Determine acidemia or alkalemia.*
Step 2: *Determine respiratory or metabolic cause.*
Step 3: *Determine compensation.*
Step 4: *Calculate AG.*
Step 5: *Determine delta gap.*

An example of the use of these steps is shown in Box 51.4.

Box 51.4 • Acid-Base Clinical Scenarios

Example 1: A woman with dual acidoses has the following blood chemistry values: $[\text{Na}^+]$, 136 mmol/L; $[\text{HCO}_3^-]$, 10 mmol/L; $[\text{Cl}^-]$, 108 mmol/L; pH 7.14; and Pco_2, 25 mm Hg.

Step 1: *Determine acidemia or alkalemia*: pH is 7.14. She has acidemia.

Step 2: *Determine respiratory or metabolic*: Check Pco_2 and serum $[\text{HCO}_3^-]$. Bicarbonate is decreased. The patient has primary metabolic acidosis.

Step 3: *Determine compensation:* If $[\text{HCO}_3^-]$ is 10 mmol/L, the expected increase in Pco_2 would be 25. ($[\text{HCO}_3^-]$ + 15). This patient's Pco_2 is 25. Respiratory compensation is therefore appropriate.

Step 4: *Calculate AG*: ($[\text{Na}^+] - [\text{Cl}^-] + [\text{HCO}_3^-]$) equals 20 mmol/L—10 mmol/L above the normal range.

Step 5: *Delta gap*: The increase in AG above normal is 10 mmol/L. In this case, the change in AG and bicarbonate is in a ≈1:1 ratio. Therefore, the expected serum $[\text{HCO}_3^-]$ should be ≈14 mmol/L, a decrease of 10 mmol/L. However, this patient's $[\text{HCO}_3^-]$ is 10 mmol/L, lower than expected. This additional decrease in $[\text{HCO}_3^-]$ indicates a second primary acidosis (normal AG acidosis due to diarrhea) in addition to the lactic acidosis.

Example 2: A patient is being treated with nasogastric suction. He has an acid-losing metabolic alkalosis (due to the suction). Subsequently, septic shock develops. Laboratory studies show an increased AG, and his lactate level becomes increased. Blood studies show: $[\text{Na}^+]$, 140 mmol/L; $[\text{Cl}^-]$, 90 mmol/L; and $[\text{HCO}_3^-]$, 25 mmol/L.

The values appear benign, but calculating the AG (140–90–25=25 mmol/L) shows that the patient has a high AG acidosis. Given that the AG is 15 mmol/L above the normal range, his expected $[\text{HCO}_3^-]$ should be 10 mmol/L (decreased by 15 mmol/L). His $[\text{HCO}_3^-]$ is normal because he has a superimposed metabolic alkalosis from the nasogastric suction. In this case, the blood pH will most likely be within the reference range.

Abbreviation: AG, anion gap.

52 Acute Kidney Injury

SUZANNE M. NORBY, MD; KIANOUSH B. KASHANI, MD, MS

Definition

Acute kidney injury (AKI) denotes a rapid deterioration of kidney function within 1 week of an insult to the kidney. AKI results in the accumulation of nitrogenous metabolites, along with fluid, electrolyte, and acid-base imbalances.

AKI is described by the KDIGO (Kidney Disease: Improving Global Outcomes) group using a 3-stage definition (Table 52.1). The criteria for stage 1 (least severe) AKI are: 1) an absolute increase in serum creatinine (SCr) value by at least 0.3 mg/dL from baseline within 48 hours; *or* 2) a relative increase in SCr to 1.5 to 1.9 times baseline within the past 7 days; *or* 3) urine output decreased to less than 0.5 mL/kg/h for 6 to 12 hours. The use of SCr as a marker of AKI, however, has disadvantages. For example, many conditions interfere with SCr measurement and, therefore, can overestimate or underestimate the actual GFR (Table 52.2). Changes in blood urea nitrogen are not included in the diagnostic criteria for AKI. Novel functional and injury biomarkers of AKI are now used for early recognition of AKI, estimation of the intensity of injury, and prognosis for recovery. A relatively common functional biomarker used for GFR estimation is cystatin C, which is synthesized by all nucleated cells and released into the blood at a relatively constant rate. As with SCr, factors other than GFR influence the cystatin C level (Table 52.2).

The traditional classification system subdivides AKI into prerenal, intrinsic renal, and postrenal categories (Figure 52.1). Although AKI has a dominant cause in some patients, multiple factors usually contribute to its development.

Prerenal AKI

Definition

Prerenal AKI is defined as decreased GFR *without* ischemic injury to tubules. Prerenal AKI can result from disruption of several heterogeneous pathophysiologic mechanisms that may require different management strategies (Box 52.1). All the prerenal types are characterized by decreased effective blood volume.

Causes of Prerenal AKI

Intravascular volume depletion is one cause of prerenal AKI. It could be due to external loss of fluids and electrolytes (vomiting,

Table 52.1 • Classification and Staging System for Acute Kidney Injury

Stage	Serum Creatinine Concentration	Urine Output
1	Increase of ≥0.3 mg/dL *or* Increase to 1.5-1.9 times baseline	<0.5 mL/kg/h for 6-12 h
2	Increase to 2.0-2.9 times baseline	<0.5 mL/h for ≥12 h
3	Increase to 3.0 times baseline *or* Increase to ≥4.0 mg/dL *or* Initiation of renal replacement therapy	<0.3 mL/kg/h for ≥24 h *or* anuria for ≥12 h

Modified from Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012 Mar;2(1):1-138; used with permission.

Table 52.2 • Conditions That Change Analyte Levels Independently of GFR

Analyte	GFR-Independent Increase	GFR-Independent Decrease
Serum creatinine	Decreased tubular secretion Trimethoprim Cimetidine Amiloride Probenecid Spironolactone Triamterene Male sex Rhabdomyolysis Vigorous exercise Large muscle mass Ingestion of cooked meat Increased muscle mass Jaffe reaction Ketotic states Hyperglycemia	Low muscle mass Small body habitus Female sex Amputation Advanced age Advanced liver disease Muscle wasting disorders Neuromuscular diseases Malnutrition Dietary protein restriction Chronic kidney disease Liver disease Vegetarian diet Amputation Jaffe reaction Hyperbilirubinemia
Blood urea nitrogen	Hypercatabolism High-protein diet Decreased intravascular volume Diuretics Glucocorticoids Tetracyclines Gastrointestinal tract bleeding	Aggressive volume expansion Pregnancy SIADH Dietary protein restriction Liver disease
Cystatin C	Advanced age Male sex Greater body mass Smoking Inflammatory states Hyperthyroidism	Female sex Lower body mass Corticosteroids Hypothyroidism

Abbreviations: GFR, glomerular filtration rate; SIADH, syndrome of inappropriate antidiuretic hormone.

From Bagshaw SM, Gibney RTN. Conventional markers of kidney function. Crit Care Med. 2008 Apr;36(Suppl 4):S152-8; used with permission.

diarrhea, and dehydration), loss of plasma volume (burns), internal fluid losses (third spacing, as occurs in severe pancreatitis), or hemorrhage. Physical findings of volume depletion include orthostatic hypotension, dry mucous membranes, and decreased skin turgor. Management involves intravascular fluid expansion.

Decreased cardiac output, as occurs in congestive heart failure or right ventricular failure (cardiorenal syndrome), also can cause prerenal AKI. Physical findings include increased jugular venous pressure, bibasilar crackles in the lungs, peripheral edema, and a third heart sound gallop. Management consists of optimization of cardiac function, which often includes the use of diuretics.

Peripheral vasodilatation and abnormal vascular tone during sepsis, along with the effects of inflammatory mediators, could result in prerenal AKI; without appropriate management, this would lead to acute tubular injury. Intra-abdominal hypertension, sometimes referred to as abdominal compartment syndrome, also can cause impaired perfusion to the kidneys. Conditions that increase intra-abdominal pressure include large-volume ascites, ileus, interstitial fluid accumulation (as occurs during resuscitation with large volumes of blood products or fluids), trauma, and abdominal surgery.

Renal artery occlusion due to thrombosis, stenosis, emboli, or vasculitis of the main renal arteries or several intrarenal arteries can result in a rapid decline in kidney function. If not promptly addressed, renal artery occlusion causes ischemic acute tubular necrosis (ATN).

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase and decrease vasodilatory prostaglandin production. Patients who take NSAIDs and have underlying CKD, volume depletion, advanced liver disease, or congestive heart failure are at risk for AKI. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) increase the risk of AKI when renal blood flow is decreased. These medications interfere with the action of angiotensin II, which serves to maintain GFR when renal blood flow is decreased. If AKI

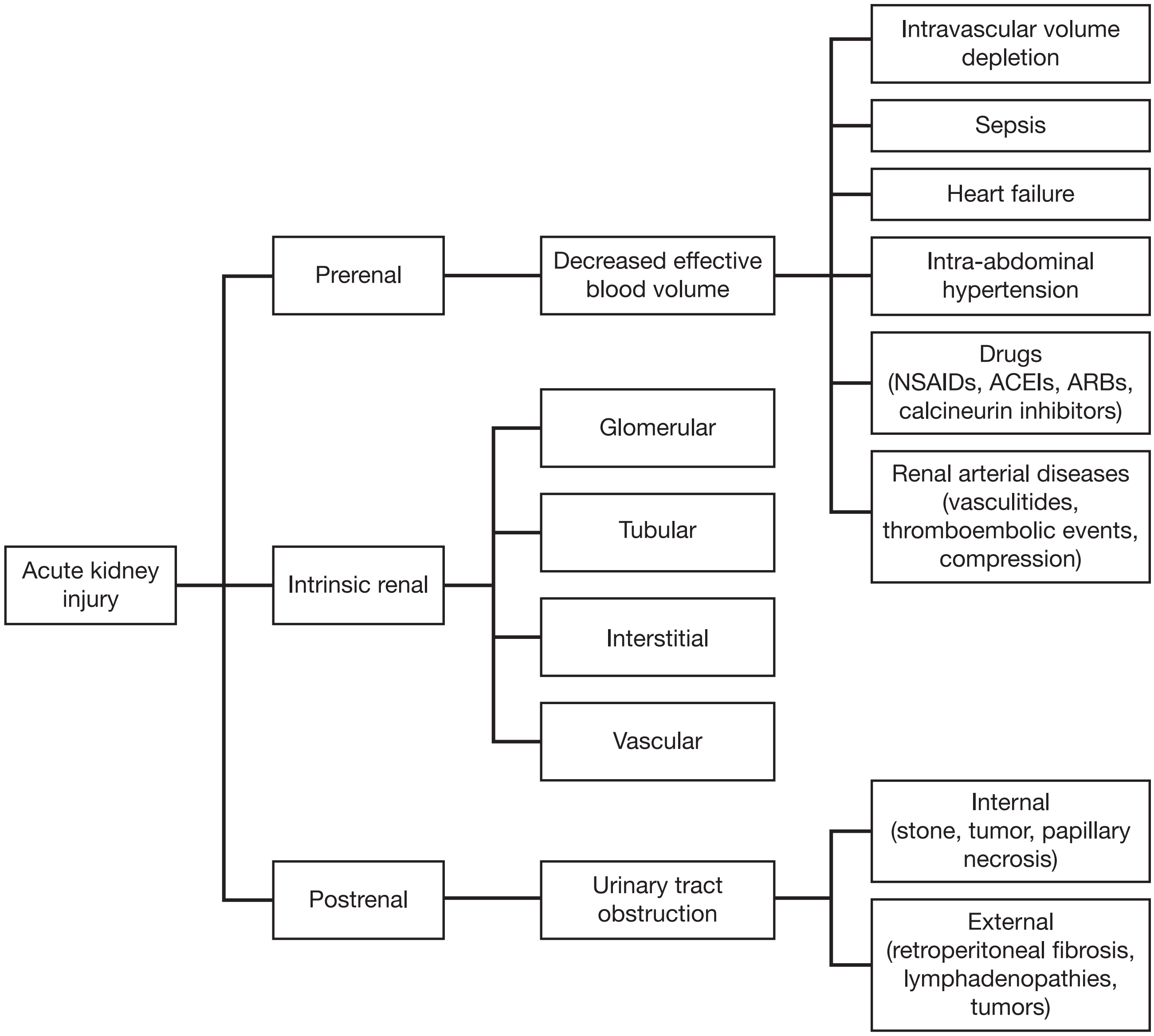
Acute kidney injury
Prerenal
Intrinsic renal
Postrenal
Decreased effective blood volume
Intravascular volume depletion
Sepsis
Heart failure
Intra-abdominal hypertension
Drugs (NSAIDs, ACEIs, ARBs, calcineurin inhibitors)
Renal arterial diseases (vasculitides, thromboembolic events, compression)
Glomerular
Tubular
Interstitial
Vascular
Urinary tract obstruction
Internal (stone, tumor, papillary necrosis)
External (retroperitoneal fibrosis, lymphadenopathies, tumors)

Figure 52.1. *Classification of Acute Kidney Injury. Acute kidney injury is traditionally classified as prerenal (functional), intrinsic renal, and postrenal. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAID, nonsteroidal anti-inflammatory drug.*

Box 52.1 • Characteristics of Prerenal Acute Kidney Injury

Increased reabsorption of sodium and water leading to concentrated urine

Increased reabsorption of urea resulting in increase of BUN out of proportion to creatinine (BUN:creatinine ratio >20:1)

Rapid reversibility if the underlying cause is treated

Abbreviation: BUN, blood urea nitrogen.

develops while a patient is taking an ACEI or ARB, the medication should be withheld until kidney function improves. Also, drugs in the calcineurin inhibitor class of immunosuppressants (eg, cyclosporine and tacrolimus) cause renal vasoconstriction and kidney hypoperfusion.

Hepatorenal syndrome (HRS), another cause of prerenal AKI, is a rapid decline in kidney function in the presence of severe liver disease. HRS is a functional kidney dysfunction induced by intrarenal vasoconstriction in the presence of circulatory failure with splanchnic vasodilatation and relatively insufficient cardiac output, which leads to a decrease in the effective blood volume.

Box 52.2 • Diagnostic Criteria for Hepatorenal Syndrome in Patients With Hepatic Failure and Portal Hypertension

Diagnosis of cirrhosis and ascites

AKI

No improvement in SCr level after 2 d of diuretic withdrawal and volume expansion with albumin (1 g/kg per d)

No other apparent reason for AKI, such as recent administration of nephrotoxic drugs or shock

No signs of structural kidney injury, defined as:

- Absence of proteinuria >500 mg/d
- Absence of microhematuria >50 RBCs per high-power field
- Normal findings on renal ultrasonography

Abbreviations: AKI, acute kidney injury; RBC, red blood cell; SCr, serum creatinine.

Precipitating events may be worsening liver function, bleeding, infection (such as spontaneous bacterial peritonitis), and large-volume paracentesis without albumin replacement. Diagnostic criteria for HRS in patients with hepatic failure and portal hypertension are listed in Box 52.2.

Key Definition

Hepatorenal syndrome: *functional kidney failure associated with severe liver disease and induced by intrarenal vasoconstriction with circulatory dysfunction, splanchnic vasodilatation, insufficient cardiac output, and hypovolemia.*

In type 1 HRS, the development of kidney dysfunction is rapid; type 2 HRS manifests as a more gradual decrease in kidney function and, often, refractory ascites. Administration of albumin and vasoconstrictors (such as vasopressin analogues) or midodrine plus octreotide may improve the historically poor short-term prognosis. Transjugular intrahepatic portosystemic shunt placement may also improve HRS. Liver transplant is the preferred therapy for appropriate candidates.

KEY FACTS

- ✓ AKI—common (incidence is increasing) and associated with considerable morbidity and mortality
- ✓ Cystatin C—relatively common biomarker for estimating GFR
- ✓ Type 1 HRS—rapid decline in kidney function
- ✓ Type 2 HRS—gradual decline in kidney function, often with refractory ascites

Intrinsic Renal AKI

Glomerular

Glomerular disease occurring in combination with AKI, termed *rapidly progressive glomerulonephritis*, and vasculitis are discussed in Chapter 55, "Renal Parenchymal Diseases."

Tubular

Acute Tubular Necrosis

The natural history of ATN depends on its cause, which can be inflammation, nephrotoxic injury, or, less frequently, ischemia (from decreased oxygen delivery). Many toxins, both endogenous and exogenous, can cause tubular damage. The timeline of ATN development and recovery is based on the severity of acute illness and number of insults. If prerenal AKI lasts long enough, overt tubular damage ensues (initiation phase). Extension in severity of the injury after reperfusion is usually from the infiltration of inflammatory cells. The typical course of ischemic ATN begins with a rapid decrease in urine output, accompanied by an increase in the SCr level (Figure 52.2). During the maintenance phase, oliguria is usually followed by polyuria before tubules regain their concentrating capacity. In the recovery phase, the SCr level begins to decrease and urine output normalizes. In a substantial proportion of patients with ATN, even after apparent complete recovery, CKD develops, which could lead to end-stage renal disease.

One specific type of ATN is **contrast-associated AKI**, which is typically defined as an increase in the SCr value by 0.5 mg/dL or 25% within 3 days after administration of a contrast agent if no other cause is identified. In most patients, urine output

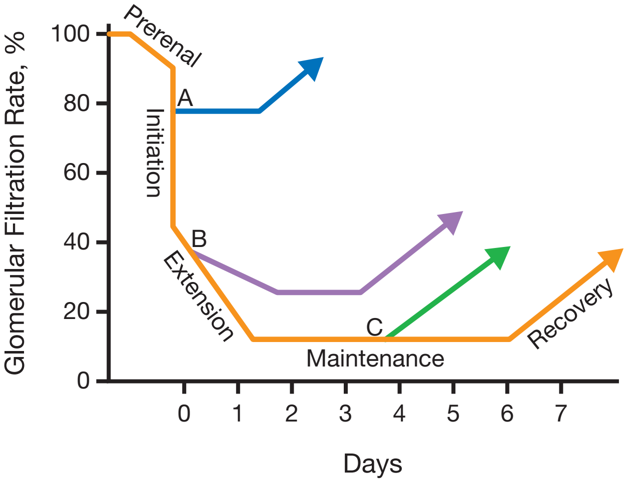

Figure 52.2. Time Course of Acute Tubular Necrosis. A, B, and C indicate therapy for preventing initiation (A), therapy for limiting the extension phase (B), and therapy for established acute tubular necrosis (C).

(From Molitoris BA. Transitioning to therapy in ischemic acute renal failure. J Am Soc Nephrol. 2003 Jan;14[1]:265-7; used with permission.)

decreases and SCr level increases 24 to 48 hours after administration of the dye and returns to normal within 7 to 10 days. Limiting other modifiable risk factors for AKI and optimizing intravascular volume are associated with a decrease in the incidence of contrast-associated AKI (Box 52.3).

Key Definition

Contrast-associated acute kidney injury: *Increase in serum creatinine value by 0.5 mg/dL or 25% within 3 days after contrast agent administration if no other cause is identified.*

Tubular cells can be directly damaged by many medications and agents, including aminoglycosides, amphotericin B, vancomycin, calcineurin inhibitors, cisplatin, methotrexate, ifosfamide, pentamidine, contrast agents, foscarnet, and cidofovir.

Pigment Nephropathy

Pigment nephropathy can occur with rhabdomyolysis or intravascular hemolysis, in which abnormal amounts of myoglobin or free hemoglobin in the serum are filtered by the kidney. These pigments are directly toxic to renal tubular cells and can also form intratubular casts. The key to diagnosis of pigment nephropathy is a positive finding of blood on a urine dipstick test without finding red blood cells (RBCs) on urine microscopy. During rhabdomyolysis or hemolysis, management includes aggressive intravenous isotonic fluid administration, with or without loop diuretics, to achieve a urine output of 200 to 300 mL/h. Urine alkalization has been advocated but is controversial and generally not recommended.

Box 52.3 • Contrast-Associated AKI Risk Factors and Risk Modification

Risk factors for contrast-associated AKI:
- Advanced age
- Diabetes mellitus
- CKD (especially with estimated GFR <30 mL/min/1.73 m^2)
- Congestive heart failure
- Acute myocardial infarction within 24 h
- Peripheral vascular disease
- Intravascular volume depletion
- Concomitant use of other nephrotoxins

Steps to decrease the incidence or severity of contrast-associated AKI in high-risk patients:
- Use low or isosmolar contrast agents
- Limit the dose of contrast agent
- Increase the time between repeated dye loads
- Withhold medications that alter renal blood flow or intrarenal hemodynamics (ACEIs, ARBs, and NSAIDs)
- Optimize intravascular effective blood volume with intravenous isotonic crystalloid solution

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; GFR, glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drug.

Acute Uric Acid Nephropathy

Acute uric acid nephropathy is associated with the tumor lysis syndrome that develops after chemotherapy, myeloproliferative disorders, heat stroke, status epilepticus, and Lesch-Nyhan syndrome. AKI is caused by uric acid crystal formation in the renal tubular lumens, causing intrarenal tubular obstruction. This condition is generally reversible. Prevention includes forced diuresis, allopurinol, and rasburicase. In some cases, hemodialysis is needed.

Crystal Deposition–Related Kidney Disease

Medications that may cause crystal deposition include acyclovir, indinavir, sulfonamide, methotrexate (doses >50 mg/kg), and triamterene. Treatment comprises optimizing the intravascular volume, alkalizing the urine in some cases, and withdrawing the offending agents.

Excessive oxalate production occurs after ethylene glycol ingestion. Precipitation of calcium oxalate crystals contributes to AKI, which is also mediated by direct tubular toxicity of glycolate, another metabolite of ethylene glycol. Treatment consists of urine alkalization, administration of the alcohol dehydrogenase inhibitor fomepizole, and hemodialysis.

Interstitial

Acute interstitial nephritis (AIN) is an inflammatory process characterized by a mononuclear cell infiltrate within the renal interstitium. Relatively common, AIN accounts for approximately 10% to 15% of cases of AKI. AIN is idiopathic in 10% to 20% of cases, but it is most frequently associated with drugs, infections, autoimmune systemic diseases, and cancers (Box 52.4).

Diagnosis of AIN requires a kidney biopsy. Clinically, AIN has a sudden onset, usually after several days of exposure to an offending agent. Systemic manifestations of a hypersensitivity reaction in patients with drug-induced AIN include fever, maculopapular rash, and arthralgias (25% of patients). Flank pain caused by distention of the renal capsule occurs in about 50% of patients. Abnormal kidney function, occurring in about 60% of patients, varies from a mild increase in the SCr level to severe AKI requiring dialysis. Tubular damage can impair the urinary concentration mechanism and result in polyuria. Other urinary abnormalities are listed in Box 52.5. Peripheral eosinophilia is common (about 50% of patients).

Therapy for AIN includes identification and elimination of inciting factors. For patients with drug-induced AIN, early administration of corticosteroids for 2 to 4 weeks may be

Box 52.4 • Common Causes of Acute Interstitial Nephritis

- Drugs
  - Antibiotics—penicillin, methicillin (anti–tubular basement membrane antibodies), ampicillin, rifampin, sulfa drugs, ciprofloxacin, pentamidine
  - NSAIDs—not dose-dependent; recurs; possibly T-cell–mediated; allergic signs and symptoms are absent; interstitial nephritis with nephrotic syndrome and decreased kidney function may have a latent period
  - Diuretics—thiazides, furosemide, bumetanide (sulfa derivatives)
  - Cimetidine
  - Proton pump inhibitors
  - Allopurinol, phenytoin, phenindione
  - Cyclosporine
- Infections
  - Bacteria—*Legionella, Brucella, Streptococcus, Staphylococcus*, pneumococci
  - Viruses—Epstein-Barr virus, CMV, *Hantavirus*, HIV, hepatitis B virus, *Polyomavirus*
  - Fungi—*Candida, Histoplasma*
  - Parasites—*Plasmodium, Toxoplasma, Schistosoma, Leishmania*
- Systemic diseases
  - Systemic lupus erythematosus
  - Sjögren syndrome
  - Sarcoidosis
  - Lymphoma, leukemic infiltration
  - Kidney transplant rejection
- Idiopathic

Abbreviations: CMV, cytomegalovirus; NSAID, nonsteroidal anti-inflammatory drug.

Box 52.5 • Urinary Abnormalities in AIN

- Pyuria (in almost all patients)
- Microscopic hematuria
- Low-grade proteinuria (<1 g/1.73 m^2/24 h)
- Eosinophiluria (>1% eosinophils)—may be suggestive of AIN but is also seen in other unrelated kidney diseases; relatively low sensitivity and specificity limit the utility of this test

Abbreviation: AIN, acute interstitial nephritis.

beneficial. Corticosteroids are not indicated in infection-related AIN. Although AIN has traditionally been considered to be reversible, recent studies have shown that impaired kidney function can result in CKD in up to 40% of patients.

Vascular

Atheroembolic disease (a vascular type of intrinsic renal AKI) usually occurs after vascular manipulation during arterial catheterization or vascular operations in patients who have severe atherosclerosis. The timeline for development of atheroembolic disease after a procedure is variable, ranging from hours to weeks. About 20% of patients with atheroembolic disease do not report a history of vascular procedures. Livedo reticularis may be seen on the back, flank, abdomen, or extremities. On ophthalmoscopic examination, atheroemboli manifest as Hollenhorst plaques. Other clinical manifestations are bowel ischemia and AKI. Although the diagnosis is mainly clinical, the definitive diagnosis of atheroembolic disease is made by kidney or skin biopsy showing cholesterol crystals in small arterioles with distal necrosis. A high erythrocyte sedimentation rate or C-reactive protein level and decreased complement levels are suggestive of atheroembolic disease. The prognosis for kidney recovery after atheroembolic disease is poor, and recovery is usually incomplete. Treatment is supportive, including cholesterol-lowering agents and renal replacement therapy as needed. Anticoagulation is relatively contraindicated because it can destabilize atheromatous plaques and, therefore, cause additional cholesterol emboli.

Postrenal AKI

Postrenal AKI is defined as obstructed urinary flow at any level of the urinary tract. Obstruction can result from any of several causes, both internal and external (Box 52.6).

Postrenal AKI is often accompanied by pain, hypertension, and normal anion gap acidosis. Postrenal causes should be excluded in all patients with anuria. For this purpose, ultrasonography is recommended because it is noninvasive, widely available, and very sensitive for established hydronephrosis. Postrenal AKI is usually reversible with prompt relief of the obstruction. Additionally, partial or unilateral obstruction may occur without an increase in SCr level.

Box 52.6 • Causes of Urinary Flow Obstruction

- Bladder outlet obstruction (eg, prostate cancer or benign prostatic hypertrophy in men and genitourinary cancer in women)
- Neurogenic bladder
- Ureteral obstruction (eg, urolithiasis, tumor, necrosed renal papillae, and blood clots)
- Extrinsic compression of the genitourinary tract (eg, cancer and retroperitoneal fibrosis)
- Inadvertent surgical ligation of a ureter

Table 52.3 • Comparison of Test Results in Prerenal Failure and Acute Tubular Necrosis

Laboratory Test or Urinary Index	Prerenal Failure	Acute Tubular Necrosis
Urine osmolality, mOsm/kg	>500	<400
Urine specific gravity	>1.018	Approximately 1.010
Urinary sodium level, mmol/L	<20	>40
Fractional excretion of sodium, %[a]	<1	>2
Fractional excretion of urea, %	<35	>35
Urinary sediment	Normal; occasional hyaline or fine granular casts	Renal tubular epithelial cells; granular and muddy brown casts

[a] $\text{Fractional Excretion of Sodium} = \frac{[\text{Urinary Sodium}] \times [\text{Plasma Creatinine}]}{[\text{Plasma Sodium}] \times [\text{Urinary Creatinine}]} \times 100.$

Modified from Schrier RW, Wang W, Poole B, Mitra A. Acute renal failure: definitions, diagnosis, pathogenesis, and therapy. J Clin Invest. 2004 Jul;114(1):5-14. Erratum in: J Clin Invest. 2004 Aug;114(4):598; used with permission.

Diagnostic Approach to AKI

Initial Evaluation

Obtaining a medical history and performing a physical examination are the first steps in distinguishing the causes of AKI. Past medical history is important for identifying risk factors such as diabetes mellitus, hypertension, CKD, allergies, and medications, along with any family history of kidney disease. Physical signs and symptoms of AKI are nonspecific and can include polyuria, oliguria, anuria, hematuria, dysuria, decreased appetite, nausea and vomiting, altered mental status, increased respiratory rate due to respiratory compensation, hypervolemia, and hypertension.

The physical examination should assess fluid balance to distinguish between prerenal causes and intrinsic or postrenal causes.

Laboratory Studies

Findings on urinalysis and urine chemistry testing can help to distinguish among causes of AKI (Table 52.3). In prerenal AKI, urine osmolality is increased, and the urinary sediment findings are usually benign, with only hyaline casts. Urinary sodium level and fractional excretion of sodium are low because sodium is retained by the kidney in states of low renal perfusion. In ATN, urine is usually isosmotic with the serum. Fractional excretion of sodium is of low utility in patients who are not oliguric.

Although examination of urinary sediment has low sensitivity, specificity is high for kidney disorders. Specific urine microscopic findings in ATN are renal tubular epithelial cells, granular casts, and epithelial cell casts. In AIN, leukocytes, leukocyte casts, and urinary eosinophils can be found. Dysmorphic RBCs and RBC casts indicate glomerular bleeding, consistent with glomerulonephritis or other damage to the glomerular basement membrane. With severe glomerular inflammation, leukocytes and leukocyte casts may also be seen. Nondysmorphic RBCs may suggest obstruction due to genitourinary cancer or urolithiasis.

Imaging

Ultrasonography can be helpful in distinguishing among the causes of AKI (Table 52.4). For postrenal AKI, ultrasonography is the test of choice to determine whether hydronephrosis is present. If the use of contrast media is avoided, other imaging techniques can be useful on a case-by-case basis.

Biopsy

Kidney biopsy, as the diagnostic standard for AKI, is often indicated when renal parenchymal involvement is suspected, such as when

Table 52.4 • Use of Ultrasonography in Differential Diagnosis of AKI

Ultrasonographic Finding	Diagnosis
Shrunken kidneys	Chronic kidney disease
Normal-sized kidneys	
Echogenic	Acute glomerulonephritis Acute tubular necrosis
Normal echocardiographic pattern	Prerenal AKI Acute renal artery occlusion
Enlarged kidneys	Cancer Renal vein thrombosis Diabetic nephropathy HIV-associated nephropathy
Hydronephrosis	Obstructive nephropathy

Abbreviation: AKI, acute kidney injury.

Modified from Lameire N, Van Biesen W, Vanholder R. Epidemiology, clinical evaluation, and prevention of acute renal failure. In: Feehally J, Floege J, Johnson RJ, editors. Comprehensive clinical nephrology. 3rd ed. Philadelphia (PA): Mosby Elsevier; c2007. p. 771-85; used with permission.

a patient has a rapid decline in kidney function in the presence of progressive or massive proteinuria or abnormal urinary sediment findings that include glomerular hematuria (RBC casts or dysmorphic RBCs), granular casts, sterile pyuria, and/or leukocyte casts. In addition, clinicians may choose kidney biopsy when progressive kidney dysfunction is unexplained by noninvasive testing.

Biomarkers

Since the early 2000s, many tubular cell injury biomarkers have been discovered. Proteins such as NGAL (neutrophil gelatinase-associated lipocalin), KIM-1 (kidney injury molecule-1), and IGFBP7·TIMP2 (insulin-like growth factor binding protein 7 and tissue inhibitor metalloproteinase 2) could potentially be used for the early diagnosis of AKI.

Management of AKI

The management of AKI is mostly supportive because no therapeutic options are currently available. Determining and managing the risk factors associated with AKI are essential steps to decrease the extent of the injury (Box 52.7).

KEY FACTS

- ✓ Urinary sediment examination for kidney disorders—very specific but not sensitive
- ✓ Oliguria—measurement of fractional excretion of sodium helps distinguish prerenal AKI from ATN
- ✓ Kidney biopsy—indicated when renal parenchymal diseases are suspected from history, physical examination, and urinary sediment findings
- ✓ Management of AKI—early diagnosis and risk factor mitigation with mainly supportive therapy

If renal replacement therapy is used for AKI, the goals are to maintain fluid, electrolyte, acid-base, and solute balance and to prevent further insult and promote healing. Renal replacement therapy should be considered for patients who have diuretic-resistant volume overload, severe electrolyte disorders (hyperkalemia with electrocardiographic changes), acid-base disturbances, and uremic symptoms (metabolic encephalopathy, pericarditis, and bleeding).

Box 52.7 • Management Recommendations According to the Stage of AKI

- High risk for AKI
  - Discontinue all nephrotoxic agents when possible
  - Ensure volume status and perfusion pressure
  - Consider functional hemodynamic monitoring
  - Monitor serum creatinine level and urine output
  - Avoid hyperglycemia
  - Consider alternatives to radiocontrast procedures
- Stage 1
  - All the above *and*
  - Perform noninvasive diagnostic work-up
  - Consider invasive diagnostic work-up
- Stage 2
  - All the above *and*
  - Check for changes in drug dosing
  - Consider renal replacement therapy
  - Consider admission to intensive care unit
- Stage 3
  - All the above *and*
  - Avoid the use of subclavian catheters if possible

Abbreviation: AKI, acute kidney injury.

Modified from Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012 Mar;2(1):1-138; used with permission.

53 Chronic Kidney Disease

CARRIE A. SCHINSTOCK, MD

Epidemiology

Chronic kidney disease (CKD) is a worldwide public health problem. In the United States, the prevalence of end-stage renal disease (ESRD) is increasing, especially among persons older than 65 years. More than 20 million people in the United States are thought to have CKD, and this population uses a disproportionate amount of health care resources. CKD is also associated with an increased risk of death, particularly from cardiovascular causes.

Certain ethnic groups have an increased incidence of CKD. In the United States, African Americans have the highest incidence of CKD, followed by American Indians and Alaskan natives; Asian Americans, native Hawaiians, and other Pacific Islanders; Hispanics; and whites. The main risk factors for the development of CKD include diabetes mellitus and hypertension. Other major causes include glomerulonephritis, inherited disorders such as polycystic kidney disease, congenital urologic abnormalities, renal obstruction, and autoimmune disease.

Definition and Staging

Kidney damage refers to abnormal renal histologic findings, abnormal urine sediment (ie, white or red blood cell casts), or albuminuria (>30 mg/dL). **Chronic kidney disease** is defined by the presence of kidney damage or decreased kidney function (as indicated by decreased glomerular filtration rate [GFR]) for 3 or more months.

Key Definition

Kidney damage: *abnormal renal histologic findings, abnormal urine sediment (ie, white or red blood cell casts), or albuminuria (>30 mg/dL).*

Key Definition

Chronic kidney disease: *kidney damage or decreased kidney function (as indicated by decreased GFR) for ≥3 months.*

GFR is most often estimated with various equations that are based on the serum creatinine level in some combination with age, sex, race, and body size (Box 53.1). The use of serum creatinine value alone is not optimal for assessing the level of kidney function. Currently, the most commonly used equation is the Modification of Diet in Renal Disease (MDRD) Study equation. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is more reliable for patients with GFR greater than 60 mL/min/1.73 m^2 and is increasingly being used, but it is still being validated and has not been implemented for widespread use. The Cockcroft-Gault formula was historically used most often, but it is considered less accurate than the MDRD equation in many cases.

Although the standard method for assessing GFR is based on measuring the clearance of exogenous substances, such as inulin, iothalamate, and other radiolabeled markers, methods of determining estimated GFR (eGFR) provide the best overall index of kidney function because they are readily available and have been most fully evaluated. The serum concentration of cystatin C is another marker of kidney function that is not completely validated for regular use in clinical practice. Calculating 24-hour creatinine clearance with serum creatinine level and 24-hour urine collection is also suboptimal because of the tubular secretion of creatinine, especially with kidney dysfunction, and the difficulty in obtaining a reliable, timed urine collection. All these equations are unreliable in children, patients with unstable creatinine concentrations, and patients with extremes in muscle mass or diet.

Box 53.1 • Equations for Estimating Glomerular Filtration Rate

MDRD Study equation

$$\mathrm{eGFR}\left(\mathrm{mL/min/1.73\ m^2}\right) = 175 \times \mathrm{SCr}^{-1.154} \times \mathrm{Age}^{-0.203} \times 0.742\ (\text{if Female}) \times 1.212\ (\text{if African American})$$

CKD-EPI equation

$$\mathrm{eGFR} = 141 \times \min(\mathrm{SCr}/\kappa, 1)^{\alpha} \times \max\left(\mathrm{SCr}/\kappa, 1\right)^{-1.209} \times 0.993^{\mathrm{Age}} \times 1.018(\text{if Female}) \times 1.159(\text{if African American})$$

κ is 0.7 for females and 0.9 for males

α is −0.329 for females and −0.411 for males

min indicates the minimum of SCr/κ or 1

max indicates the maximum of SCr/κ or 1

Cockroft-Gault formula

$$\mathrm{eGFR} = 0.85(\text{if Female}) \times \left(\left[140 - \mathrm{Age}\right]/\mathrm{SCr}\right) \times \left(\text{Weight in kg}/72\right)$$

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine value (in mg/dL).

Data from United States Renal Data System, 2014 Annual Data Report: Epidemiology of Kidney Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2014.

CKD and albuminuria are classified in stages to help guide management. CKD is staged from 1 to 5 (Table 53.1), and albuminuria is staged from 1 to 3 (Table 53.2). A patient is considered to have ESRD when dialysis is required.

Table 53.1 • Stages of Chronic Kidney Disease

Stage	GFR, mL/min/1.73 m^2
1	>90[a]
2	60-89
3a	45-59
3b	30-44
4	15-29
5	<15

Abbreviation: GFR, glomerular filtration rate.

[a] With signs of kidney damage (eg, proteinuria).

Table 53.2 • Stages of Albuminuria

Stage	Albumin Excretion Rate, mg/24 h
1	<30
2	30-300
3	>300

Screening for CKD in High-Risk Patients

There is insufficient evidence to support screening for CKD in asymptomatic adults. However, screening can be considered for patients who are at high risk for CKD. Clinical factors that increase the risk of CKD include diabetes mellitus, hypertension, autoimmune disease, systemic infection, urinary tract infection, nephrolithiasis, urinary tract obstruction, malignant process, family history of CKD, history of acute kidney injury (AKI), small kidney mass (ie, low birth weight), or exposure to certain drugs (ie, amphotericin). Other factors include being elderly, being in an ethnic minority, or having a low socioeconomic status. Monitoring blood pressure and serum creatinine and urine albumin levels are reasonable screening tests for patients at higher risk.

Management of CKD

The general management approach to CKD includes 1) recognizing and treating reversible causes of CKD; 2) preventing progressive decrease in kidney function; 3) managing complications of CKD; 4) ensuring that medications are dosed appropriately according to GFR; 5) educating the patient about the increased risk of AKI; and 6) referring the patient to a nephrologist for management of AKI, complex CKD care, and preparation for renal replacement therapy (Box 53.2).

Box 53.2 • Approach to Management of Chronic Kidney Disease

1. Treat reversible causes of chronic kidney disease
2. Prevent worsening of kidney function
3. Manage complications of chronic kidney disease
4. Dose medications according to glomerular filtration rate
5. Educate the patient about the increased risk of acute kidney injury
6. Refer the patient to a nephrologist for management of acute kidney injury or complex chronic kidney disease, or in preparation for renal replacement therapy

Recognize and Treat Reversible Causes of CKD

Recognition of recent (<3 months) kidney dysfunction is important because it is more likely than CKD to be reversible. Major causes of AKI are summarized in Box 53.3. The diagnosis and management of AKI are reviewed in Chapter 52, "Acute Kidney Injury."

Prevent Progressive Decrease in Kidney Function

The most important step is to identify the cause of kidney dysfunction and treat it appropriately, if possible. Several factors are associated with the progression of kidney dysfunction, including proteinuria, hypertension, African American race, *APOL1* risk alleles, nephrolithiasis, low socioeconomic status, male sex, obesity, diabetes mellitus, hyperlipidemia, smoking, high-protein diet, phosphate retention, and metabolic acidosis. Often these risk factors are irreversible, and the treatment of other risk factors has not been proved to effectively decrease the progression of kidney dysfunction.

Blood pressure control, reduction in proteinuria, glycemic control (target hemoglobin A_{1c} <7%), smoking cessation, and treatment of chronic metabolic acidosis all independently prevent the progression of kidney disease. Several organizations have developed guidelines to aid in managing hypertension. Controversy exists regarding the optimal blood pressure target for patients with CKD, but most organizations support a target of 130/80 mm Hg or less in patients in this group, particularly those with known proteinuria. A recent study showed that patients with CKD who were treated intensively to achieve a target systolic blood pressure of less than 120 mm Hg had decreased mortality and cardiovascular event rates compared with patients whose systolic blood pressure target was 135 to 140 mm Hg. These results support lowering the blood pressure targets for patients with CKD. The absolute benefit of intensive blood pressure control in that study, however, was small and did not slow the decrease in kidney function. The group with intensively treated blood pressure also had increased medication burden and adverse event rates (J Am Soc Nephrol. 2017 Sep;28[9]:2812-23).

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are recommended for patients with proteinuria. These agents can be used in patients at any stage of CKD but should be started when the kidney function is stable. Serum creatinine and potassium levels should be checked 2 to 3 weeks after initiation.

Box 53.3 • Major Causes of Acute Kidney Injury

- Prerenal
  - Renovascular disease
  - Hypovolemia
  - Angiotensin-converting enzyme inhibitors
  - Angiotensin receptor blockers
  - Nonsteroidal anti-inflammatory drugs
- Intrinsic renal
  - Glomerulonephritis
  - Interstitial nephritis
  - Nephrotoxic medications
  - Cystic renal disease
- Postrenal
  - Renal obstruction (prostate enlargement, kidney or bladder stones, mass lesions)
  - Congenital ureteral abnormalities

Manage Complications of CKD

Volume Overload and Sodium Disorders

In advanced stages of CKD, the kidney loses its ability to appropriately dilute or concentrate urine, which leads to disorders in sodium balance (hyponatremia or hypernatremia). Additionally, sodium retention occurs with CKD, particularly when the GFR is less than 10 mL/min/1.73 m^2. Sodium retention contributes to hypertension, edema, and congestive heart failure. Sodium restriction (<2 g daily) and diuretics are often necessary.

Hyperkalemia

Potassium excretion is impaired in advanced CKD, particularly when oliguria leads to hyperkalemia. Concomitant metabolic acidosis, which causes a shift of potassium from the intracellular space to the extracellular space, can exacerbate this electrolyte disturbance. Moreover, hyporeninemic hypoaldosteronism, which often occurs in tubulointerstitial disease and diabetes mellitus, is also associated with hyperkalemia. The mainstay of treatment is dietary potassium restriction, but loop diuretics and potassium-binding resins are occasionally needed. Complete review of prescription and nonprescription medications is also necessary. Drugs that are commonly associated with hyperkalemia include ACE inhibitors, trimethoprim-sulfamethoxazole, ARBs, potassium-sparing diuretics, β-blockers, aldosterone antagonists, nonsteroidal anti-inflammatory drugs, and calcineurin inhibitors. Hyperkalemia associated with electrocardiographic change is a nephrologic emergency and an indication for dialysis if not rapidly treated medically.

KEY FACTS

✓ Stages of CKD and albuminuria—useful for guiding management

✓ Progression of kidney disease can be prevented with blood pressure control, decreasing proteinuria, glycemic control (hemoglobin A_{1c} <7%), smoking cessation, and treatment of chronic metabolic acidosis

✓ Potassium excretion—impaired in advanced CKD

Anemia of Chronic Disease

Anemia is a common complication of CKD and contributes to fatigue and decreased quality of life in patients with CKD. CKD is associated with inappropriate erythropoietin production, but reduced bone marrow erythropoiesis and decreased iron absorption also contribute to this condition. Reduced bone marrow erythropoiesis is associated with chronic inflammation. Decreased iron absorption is also related to inflammation, which induces the liver to produce hepcidin. This protein interferes with the iron export protein ferroportin, thereby inhibiting iron absorption.

Initial diagnostic studies for patients with suspected anemia of chronic disease include 1) complete blood cell count with a differential leukocyte count, reticulocyte index, and peripheral smear and 2) serum iron studies, including serum iron level, total iron-binding capacity, and transferrin saturation. Anemia of chronic disease in the absence of other causes of anemia is normocytic and normochromic. The serum iron concentration and transferrin level (also measured as total iron-binding capacity) are both low, and the transferrin saturation is usually normal or low-normal. In contrast, with iron deficiency the transferrin level is increased and transferrin saturation is low. Ferritin is an unreliable marker of iron stores in CKD because it can be increased in the presence of inflammation. A coexisting iron deficiency is often present.

Treatment of anemia in patients with CKD who are not receiving dialysis should be limited mainly to those with symptoms. Treatment includes erythropoietin-stimulating agents, red blood cell transfusion, or supplemental iron if needed (parenteral iron is most effective because gastrointestinal absorption of iron is abnormal in CKD). Erythropoietin-stimulating agents are associated with thromboembolism; therefore, these agents should not be used if the hemoglobin value decreases to 12 g/dL.

Metabolic Acidosis

Metabolic acidosis is a common complication of CKD and occurs as a result of decreased ammonium excretion, retention of hydrogen ions, and reduced excretion of titratable acid. The prevalence of metabolic acidosis increases as the stage of CKD increases: A bicarbonate concentration less than 22 mmol/L is present in less than 5% of patients with stage 1 CKD, but it is present in approximately 25% of patients with stage 5 CKD who are not yet receiving dialysis. Lower serum bicarbonate level has been associated with a higher risk of progressive kidney dysfunction in several observational and randomized studies.

Mineral and Bone Disorders

CKD results in disordered calcium and phosphorus metabolism, which leads to a broad spectrum of disorders, including hyperparathyroidism (Figure 53.1), abnormal bone turnover, and vascular and soft tissue calcification (Table 53.3). Calcium and phosphorus homeostasis can be restored as the parathyroid increases the release of parathyroid hormone (PTH) in response to hypocalcemia from reduced production of calcitriol (also called 1,25-dihydroxycholecalciferol or dihydroxyvitamin D_3) and in response to hyperphosphatemia from decreased renal excretion of phosphate.

PTH is a calcemic hormone that targets the kidney, bone, and gastrointestinal tract and promotes calcium conservation by increasing reabsorption of calcium, promoting calcitriol synthesis, increasing calcium efflux from bone, and increasing calcium absorption from the gastrointestinal tract. In addition, PTH leads to decreased phosphorus absorption by the kidney, increased phosphorus absorption by the gastrointestinal tract, and increased phosphorus efflux from bone. The main phosphaturic hormone is fibroblast growth factor 23 (FGF23). Over time, hyperparathyroidism can lead to bone conditions including high bone turnover, osteitis fibrosis, defective mineralization (osteomalacia), and low bone turnover–adynamic bone disease. These bone defects can result in fractures. Besides having detrimental effects on bone, hyperparathyroidism leads to calcification of soft tissues, blood vessels, heart valves, and skin. Increased cardiovascular calcification is thought to be involved in the increased cardiovascular mortality rate of patients with CKD, particularly ESRD. One of the most severe forms of calcification is calcemic uremic arteriopathy or calciphylaxis—a form of vascular calcification characterized by extensive calcifications of the skin, muscles, and subcutaneous tissues leading to ulcerations and necrosis.

Phosphate retention in CKD leads to an increase in serum FGF23, which increases urinary phosphorus excretion and thereby maintains serum phosphorus levels. This biomarker is increased in the early stages of CKD before alterations in PTH or serum phosphorus are detected. FGF23 also leads to decreased levels of calcitriol.

Monitoring for hyperparathyroidism involves regular measurement of calcium, phosphorus, PTH, and calcitriol levels. Treatment is aimed at normalizing the levels of serum calcium, phosphate, and PTH while minimizing the risks of therapy. In addition to dietary phosphorus restriction, other commonly used therapies are phosphorus binders, vitamin D metabolites, calcimimetic agents, and parathyroidectomy.

Cardiovascular Disease

A large body of evidence indicates that patients with CKD have a substantially increased cardiovascular risk, which can be explained in part by an increase in traditional risk factors such as hypertension, diabetes mellitus, and metabolic syndrome. However, CKD alone is also an independent risk factor for cardiovascular disease. Among patients with CKD, the risk of death, particularly death due to cardiovascular disease, is much higher than the risk of eventually requiring dialysis. CKD is considered an equivalent to coronary artery disease in terms of risk of future cardiovascular events; thus, cardiovascular risk factors (diabetes mellitus, hyperlipidemia, and hypertension) should be aggressively managed.

Lipid-lowering therapy is recommended for many patients with CKD. Statin therapy or ezetimibe is recommended for patients aged 50 years or older with known kidney disease, albuminuria, or GFR less than 60 mL/min/1.73 m^2. Any patient younger than

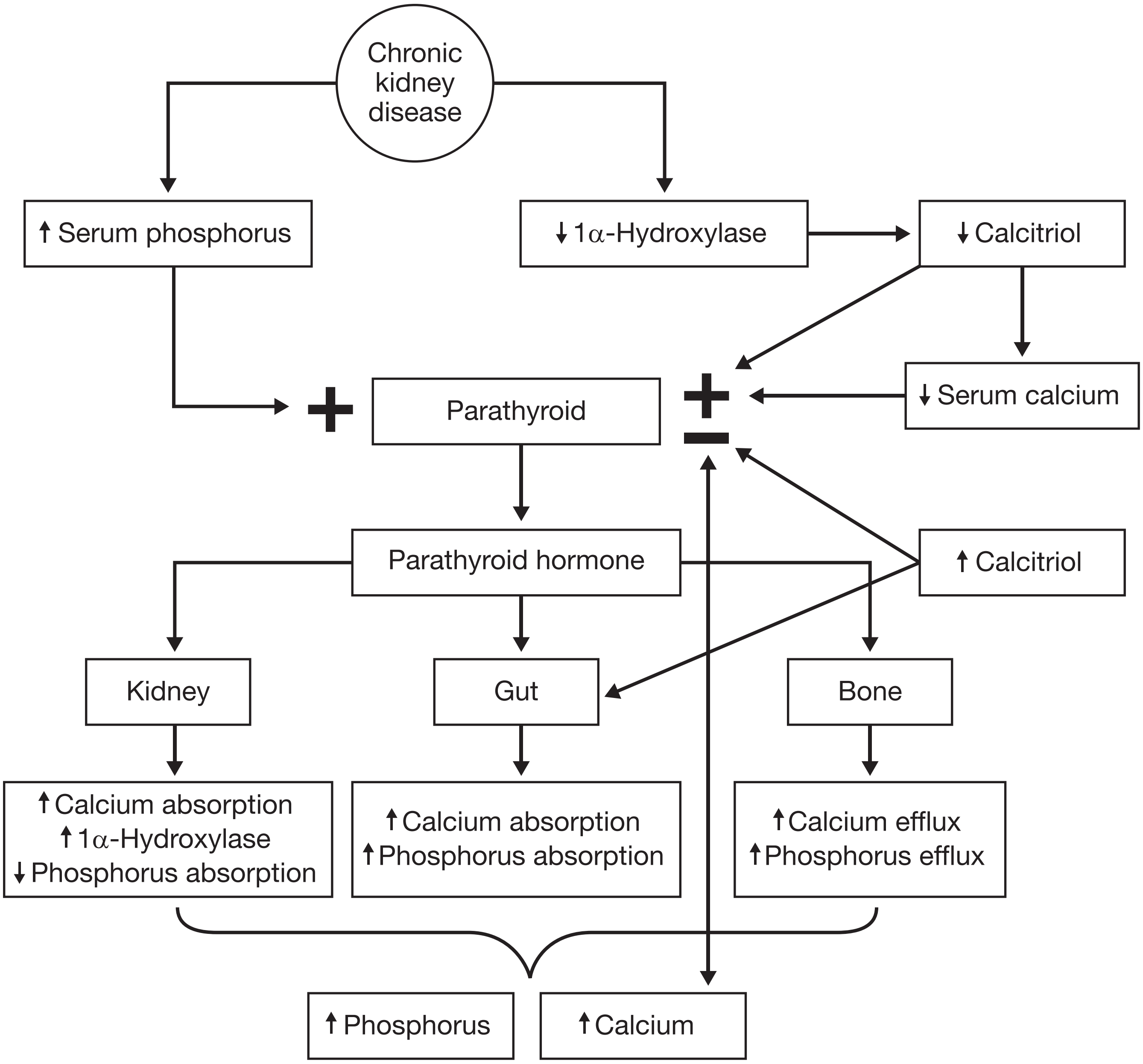
Chronic kidney disease
↑ Serum phosphorus
↓ 1α-Hydroxylase
↓ Calcitriol
↓ Serum calcium
+
Parathyroid
±
Parathyroid hormone
↑ Calcitriol
Kidney
Gut
Bone
↑ Calcium absorption
↑ 1α-Hydroxylase
↓ Phosphorus absorption
↑ Calcium absorption
↑ Phosphorus absorption
↑ Calcium efflux
↑ Phosphorus efflux
↑ Phosphorus
↑ Calcium

Figure 53.1. *Mechanisms of Hyperparathyroidism in Chronic Kidney Disease. Calcitriol is the active form of vitamin D. Plus signs indicate positive feedback; negative sign, negative feedback.*

50 years with CKD and known coronary artery disease, diabetes mellitus type 2, history of stroke, or estimated 10-year incidence of death from coronary disease or nonfatal myocardial infarction of greater than 10% should also be treated with lipid-lowering therapy. Lipid-lowering therapy should be considered in all patients who have undergone kidney transplant. Currently, evidence does not support the initiation of lipid-lowering therapy in patients with stage 5 CKD who are on dialysis, but patients in this group should not discontinue therapies started before initiation of dialysis (Am J Kidney Dis. 2015 Mar;65[3]:354-66).

Hypoalbuminemia

Hypoalbuminemia is common in patients with CKD, particularly patients with nephrotic syndrome or ESRD who are undergoing hemodialysis. In nephrotic syndrome, hypoalbuminemia results from ongoing renal protein losses. In ESRD, decreased protein synthesis and increased protein breakdown in the presence of chronic systemic inflammation is the most common cause of hypoalbuminemia. Hypoalbuminemia is a poor prognostic factor. Albumin supplementation is not beneficial in CKD.

Table 53.3 • Chronic Kidney Disease Complications Stratified by GFR[a]

	GFR, mL/min/1.73 m²				
Complication	**≥90**	**60-89**	**45-59**	**30-44**	**<30**
Anemia	4.0	4.7	12.3	22.7	51.5
Hypertension	18.3	41.0	71.8	78.3	82.1
Calcitriol deficiency	14.1	9.1	10.7	10.7	27.2
Acidosis	11.2	8.4	9.4	18.1	31.5
Hyperphosphatemia	7.2	7.4	9.2	9.3	23.0
Hypoalbuminemia	1.0	1.3	2.8	9.0	7.5
Hyperparathyroidism	5.5	9.4	23.0	44.0	72.5

Abbreviation: GFR, glomerular filtration rate.

[a] Values are percentages of affected patients.

Modified from Inker LA, Coresh J, Levey AS, Tonelli M, Muntner P. Estimated GFR, albuminuria, and complications of chronic kidney disease. J Am Soc Nephrol. 2011 Dec;22(12):2322-31; used with permission.

Cutaneous Manifestations

Pruritus, pallor, ecchymosis, and hyperpigmentation are usually signs of advanced CKD and often indicate the need for initiating dialysis. Pruritus often (but not always) improves with the initiation of dialysis. The mechanism leading to pruritus is not clear, but secondary hyperparathyroidism, dry skin, peripheral neuropathy, high aluminum levels, hyperphosphatemia, and hypervitaminosis A are potential contributors.

Neurologic Manifestations

Advanced stages of CKD are associated with several neurologic manifestations, including cognitive impairment, depression, fatigue, confusion, irritability, anxiety, and peripheral neuropathy. Indications for the initiation of dialysis include severe neurologic manifestations such as lethargy, stupor, and coma.

Uremic Syndrome

The gradual decline in function in patients with CKD is initially asymptomatic. As patients progress to ESRD, uremia is manifested by loss of appetite and weight loss, nausea, vomiting, pericarditis, peripheral neuropathy, and confusion. Severe uremia can result in seizures, coma, and death in the absence of dialysis. No direct correlation exists between signs and symptoms of ESRD and creatinine or blood urea nitrogen level.

Ensure Appropriate Dosing of Medications According to GFR

When medications excreted by the kidney are prescribed, the GFR must be estimated, usually with the various estimating equations. However, assessing kidney function with alternative methods, such as measured creatinine clearance or measured GFR with the use of exogenous filtration markers, may be useful when prescribing drugs with a therapeutic window, when eGFR and creatinine clearance provide discrepant results, or when eGFR is likely to be inaccurate or unreliable (eg, from extremes of diet, body mass, or fluctuations in GFR).

Educate Patients About Increased Risk of AKI

AKI is a risk factor not only for the development of CKD, but also for progression of CKD. Progression can occur even when kidney function appears to have recovered. The risk of progressive CKD is most pronounced in patients requiring temporary dialysis, who should be followed up by a nephrologist. Patients must be educated about the importance of avoiding known causes of preventable AKI, including nephrotoxic medications, nonsteroidal anti-inflammatory drugs, iodinated contrast agents, volume depletion, and hypotension.

KEY FACTS

- ✓ Anemia in CKD—due to inappropriate erythropoietin production, decreased bone marrow erythropoiesis, and decreased iron absorption
- ✓ Disordered calcium and phosphorus metabolism in CKD causes hyperparathyroidism, abnormal bone turnover, and vascular and soft tissue calcification
- ✓ AKI—risk factor for development and progression of CKD

Consider Referral to a Nephrologist

Referral to a nephrologist should be considered when patients have AKI, stage 4 CKD (GFR <30 mL/min/1.73 m²), substantial proteinuria (albumin-to-creatinine ratio ≥300 mg/g or protein-to-creatinine ratio >500 mg/g), unexplained hematuria or red blood cell casts, resistant hypertension, hereditary kidney disease, electrolyte abnormalities, or recurrent nephrolithiasis. Nephrologists can identify and treat causes of renal insufficiency, manage complications of CKD, and plan for renal replacement therapy with kidney transplant, dialysis (in-center hemodialysis, peritoneal dialysis, or home hemodialysis), or both transplant and dialysis.

Important indications for dialysis include metabolic acidosis, electrolyte abnormalities, ingestion of dialyzable toxic substances, volume overload that cannot be managed with diuretics, and uremic symptoms. Occasionally, dialysis can be avoided with medication management if the AKI is expected to improve, particularly if the patient is nonoliguric. However, it is especially difficult to manage hypervolemia or hyperkalemia without renal replacement therapy in the setting of anuria.

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Electrolyte Disorders[a]

QI QIAN, MD

Disorders of Sodium Balance and Volume Regulation

Disorders of sodium balance, or volume disorders, can lead to volume expansion or volume depletion. Volume expansion can be general (as in patients with congestive heart failure, cirrhosis, or nephrotic syndrome) or regional (as in patients with regional capillary leak, venous insufficiency, or lymphatic obstruction). Volume depletion is associated primarily with gastrointestinal tract (GI) fluid loss, excessive sweating, and renal sodium loss related to diuretic use or, rarely, renal salt loss.

Diagnosis

The cause of a volume disorder can be determined by physical examination. Increased systemic blood pressure with or without edema indicates total body sodium excess. In congestive heart failure and cirrhosis, the kidneys are stimulated to retain sodium because the systemic blood pressure is low from low arterial effective volume (arterial underfill) due to pump failure and circulation derangements. Sodium retention leads to a net positive sodium balance and edema. Regional volume expansion is typically obvious on physical examination: Vital signs are normal, and the areas of fluid retention are confined. Volume depletion is manifested by hypotension and tachycardia.

Therapy

Management of volume disorders is 2-fold: 1) for hypovolemia, volume repletion, and for hypervolemia, volume removal with diuretics or dialysis (or both) when appropriate, and 2) correction of the underlying causes. For patients with volume depletion, infusion of isotonic fluids and oral sodium restores volume status. In patients with congestive heart failure, measures that optimize cardiac function may improve renal perfusion and, therefore, facilitate diuresis. In cirrhosis, reduction of portal hypertension (ie, transjugular intrahepatic portosystemic shunt) and liver transplant can improve hemodynamics. In nephrotic syndrome, correcting proteinuria restores sodium homeostasis and volume balance. Diuresis, in general, is unnecessary in patients with regional fluid retention (except for regional edema involving the airway).

Disorders of Water Balance

Hyponatremia (Water Excess)

Hyponatremia—low serum sodium concentration caused by an excess of water—can be categorized as hypovolemic, euvolemic, or hypervolemic. Hypovolemia is a potent stimulus for secretion of antidiuretic hormone (ADH), also known as arginine vasopressin, which leads to renal water retention and hyponatremia. Increased plasma osmolality is the other major stimulus for ADH secretion. Euvolemic hyponatremia includes 1) psychogenic polydipsia and beer potomania, in which water or hypotonic beer ingestion exceeds the capacity of renal water excretion; 2) **syndrome of inappropriate ADH** (SIADH), in which ADH-mediated water retention is independent of serum osmolality and volume status; and, rarely, 3) hypothyroidism and adrenal insufficiency. Hypervolemic hyponatremia mainly occurs in patients with congestive heart failure or cirrhosis. Arterial underfill in both conditions signals volume depletion and activates ADH-mediated water retention, resulting in hyponatremia. In patients with moderate to advanced kidney failure, hypervolemic hyponatremia may develop because of the diminished capacity of renal water excretion.

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[a] Portions previously published in Dhondup T, Qian Q. Acid-base and electrolyte disorders in patients with and without chronic kidney disease: an update. Kidney Dis (Basel). 2017 Dec;3(4):136-48; used with permission.

Key Definition

Syndrome of inappropriate antidiuretic hormone: *ADH-mediated water retention that is independent of serum osmolality and volume status.*

Diagnosis

The initial step in evaluating patients with hyponatremia is to determine the serum osmolality. Hyperlipidemia and increased total serum protein (eg, in multiple myeloma) can cause pseudohyponatremia, in which serum osmolality is normal. Hyperglycemia can cause hyperosmotic hyponatremia. As shown in Figure 54.1, if serum osmolality is decreased (hypo-osmotic [true] hyponatremia), the differential diagnosis is narrowed to 3 categories—hypovolemic, euvolemic, or hypervolemic hyponatremia—on the basis of the patient's volume status determined by physical examination.

In patients with euvolemic hyponatremia, if the urine is not maximally diluted (>150 mOsm/kg) and the urinary sodium concentration is greater than 20 mmol/L (with a regular diet), thyroid disease and adrenal insufficiency must be ruled out before considering the diagnosis of SIADH. Patients with thiazide diuretic–induced hyponatremia may have euvolemic hyponatremia that is indistinguishable from SIADH. Clinical history is critical in establishing causation. Postoperative pain can be associated with transient SIADH. Drugs associated with euvolemic hyponatremia include selective serotonin reuptake inhibitors, carbamazepine, chlorpromazine, vasopressin analogues, 3,4-methylenedioxymethamphetamine (also called MDMA or Ecstasy), and, rarely, theophylline and amiodarone.

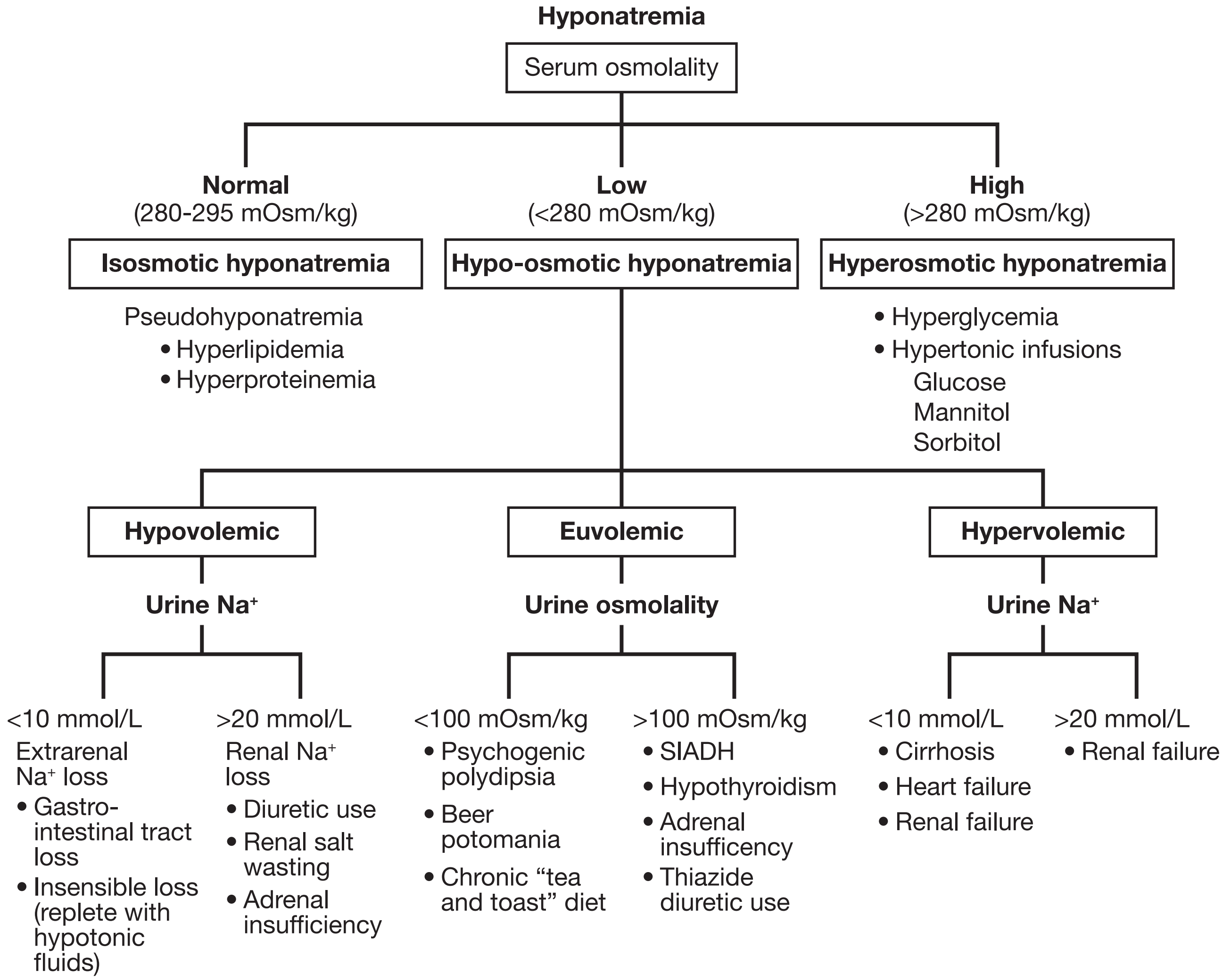
Hyponatremia
Serum osmolality
Normal
(280-295 mOsm/kg)
Low
(<280 mOsm/kg)
High
(>280 mOsm/kg)
Isosmotic hyponatremia
Hypo-osmotic hyponatremia
Hyperosmotic hyponatremia
Pseudohyponatremia
• Hyperlipidemia
• Hyperproteinemia
• Hyperglycemia
• Hypertonic infusions
Glucose
Mannitol
Sorbitol
Hypovolemic
Euvolemic
Hypervolemic
Urine Na^+
Urine osmolality
Urine Na^+
<10 mmol/L
Extrarenal Na^+ loss
• Gastrointestinal tract loss
• Insensible loss (replete with hypotonic fluids)
>20 mmol/L
Renal Na^+ loss
• Diuretic use
• Renal salt wasting
• Adrenal insufficiency
<100 mOsm/kg
• Psychogenic polydipsia
• Beer potomania
• Chronic "tea and toast" diet
>100 mOsm/kg
• SIADH
• Hypothyroidism
• Adrenal insufficiency
• Thiazide diuretic use
<10 mmol/L
• Cirrhosis
• Heart failure
• Renal failure
>20 mmol/L
• Renal failure

Figure 54.1. Diagnosis of Hyponatremia. Na^+ indicates sodium; SIADH, syndrome of inappropriate antidiuretic hormone.

Measurement of urine osmolality and urinary sodium concentration can then further help delineate the underlying cause of hyponatremia. For those eating a typical Western diet, the expected total solute excretion in adults with preserved kidney function should be greater than 800 mOsm/24 h. In those with severely reduced intake, including both salt and protein intake, which typically occurs in elderly persons on a chronic "tea and toast" diet, daily solute generation can be reduced to less than 500 mOsm/24 h. Under these circumstances, the kidney regulatory system adapts such that even moderately increased water intake to more than 3.5 L/d can induce hyponatremia because the kidneys are unable to excrete sufficient water with so little solute generated.

Total solute excretion can be estimated by multiplying urine output (in L/24 h) by urine osmolality. For example, if the patient's urine volume is 3 L/d and urine osmolality is 300 mOsm/kg, the total urine solute excretion is 900 mOsm/24 h, which indicates adequate solute generation that is sufficient to excrete water and an expected normal serum sodium concentration. In contrast, a patient with a daily urine output of 4 L and urine osmolality of 81 mOsm/kg, yielding a urine solute excretion of 324 mOsm/24 h, clearly has insufficient solutes to excrete water via urine output and thus has hypo-osmotic hyponatremia.

Therapy

For isosmotic and hyperosmotic hyponatremia, management should be directed toward correcting the underlying cause.

For hypovolemic hyponatremia, restoring intravascular volume eliminates the stimulatory signal for ADH. For patients with normal renal clearance, renal water unloading normalizes serum sodium concentration and osmolality.

For hypervolemic hyponatremia, symptomatic treatment directed toward reducing both total body water and sodium (aquaresis more than natriuresis) is necessary. Loop diuretics are usually effective. Correcting the underlying cardiac and hepatic abnormalities, if possible, will ultimately correct the water dysregulation.

For euvolemic hyponatremia, including SIADH, treatment options include restricting free water, discontinuing use of all potential contributors of hyponatremia, initiating low-dose loop diuretics in combination with oral sodium chloride, and, when symptomatic, administering high-concentration (3%) saline. Currently, lithium, demeclocycline, and long-term use of vasopressin receptor antagonists are not recommended. Specific attention should be paid to the rate of serum sodium correction. If hyponatremia develops over more than 2 days, correction should be gradual (≤10 mmol/L sodium in the first 24 hours and <18 mmol/L in the first 48 hours). Rapid correction could lead to osmotic demyelination syndrome (also known as central pontine myelinolysis), a devastating neurologic complication including quadriplegia, coma, and the "locked-in" state. Underlying causes of SIADH should always be sought and, if possible, corrected.

KEY FACTS

- ✓ Management of volume disorder—volume repletion for hypovolemia, volume removal for hypervolemia, and correction of underlying cause
- ✓ ADH secretion—stimulated by hypovolemia and by increased plasma osmolality
- ✓ Evaluation of hyponatremia—first determine serum osmolality
- ✓ Euvolemic hyponatremia—with urine osmolality >150 mOsm/kg and urinary sodium >20 mmol/L, rule out thyroid disease and adrenal insufficiency before considering SIADH
- ✓ Drugs that can cause euvolemic hyponatremia—selective serotonin reuptake inhibitors, carbamazepine, chlorpromazine, vasopressin analogues, MDMA (Ecstasy), theophylline, and amiodarone
- ✓ Serum sodium correction for hyponatremia—gradual (≤10 mmol/L in first 24 hours and <18 mmol/L in first 48 hours) to avoid osmotic demyelination syndrome

Hypernatremia (Water Deficiency)

Hypernatremia—high serum sodium concentration caused by water deficiency (Figure 54.2)—occurs with 1) decreased oral water intake (insufficient water provision or impairment of central nervous system thirst response); 2) increased renal water loss (diabetes insipidus [DI] or diuretic or aquaretic medications), osmotic diuresis from hyperalimentation, GI water loss (osmotic diarrhea), or insensible water loss (sweat and respiration); and 3) hypertonic sodium-containing fluid administration (intravenous administration of concentrated sodium bicarbonate solution). There is almost always a degree of overlap in excessive water loss and insufficient water intake. Hypernatremia occurs mostly in the elderly and infants and increases the risk of death among hospitalized patients.

Diagnosis

Unlike hyponatremia, for which confirmation of hypo-osmolality is necessary, hypernatremia is always associated with hyperosmolality; hence, there is no need to measure serum osmolality.

Urine osmolality and volume help distinguish renal from extrarenal water loss. Renal water loss is typically associated with dilute urine and high urine volume (>3 L/d), whereas extrarenal water loss is associated with maximally concentrated urine (>900 mOsm/kg) and typically low-normal urine output (<1.0-1.5 L/d).

Renal water loss can be confirmed by determining random urinary sodium and potassium concentrations. Renal water loss

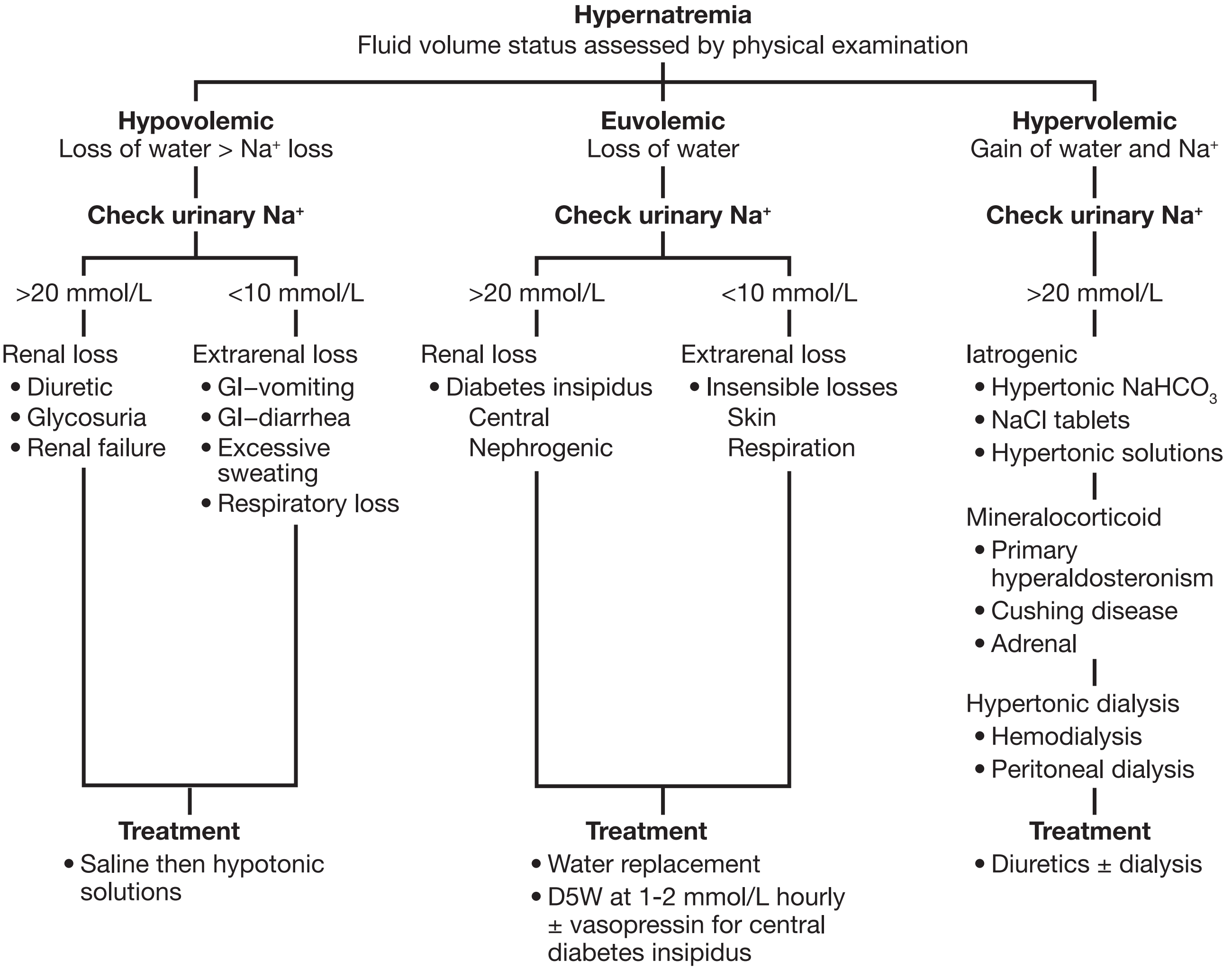
Hypernatremia
Fluid volume status assessed by physical examination
Hypovolemic
Loss of water > Na+ loss
Check urinary Na+
>20 mmol/L
<10 mmol/L
Renal loss
• Diuretic
• Glycosuria
• Renal failure
Extrarenal loss
• GI–vomiting
• GI–diarrhea
• Excessive sweating
• Respiratory loss
Treatment
• Saline then hypotonic solutions
Euvolemic
Loss of water
Check urinary Na+
>20 mmol/L
<10 mmol/L
Renal loss
• Diabetes insipidus
Central
Nephrogenic
Extrarenal loss
• Insensible losses
Skin
Respiration
Treatment
• Water replacement
• D5W at 1-2 mmol/L hourly ± vasopressin for central diabetes insipidus
Hypervolemic
Gain of water and Na+
Check urinary Na+
>20 mmol/L
Iatrogenic
• Hypertonic NaHCO3
• NaCl tablets
• Hypertonic solutions
Mineralocorticoid
• Primary hyperaldosteronism
• Cushing disease
• Adrenal
Hypertonic dialysis
• Hemodialysis
• Peritoneal dialysis
Treatment
• Diuretics ± dialysis

Figure 54.2. Diagnosis and Management of Hypernatremia. D5W indicates 5% dextrose in water; GI, gastrointestinal tract; Na^+, sodium; NaCl, sodium chloride; $NaHCO_3$, sodium bicarbonate.

is confirmed if the sum of the urinary sodium and potassium concentrations is less than the serum sodium concentration.

Osmotic Diuresis

Patients with osmotic diuresis may have polyuria and hypernatremia. The osmolality of their urine is typically similar to the plasma osmolality. Osmotic diuresis can be confirmed by calculating the total daily solute excretion. Normal solute excretion for an adult is approximately 700 to 1,000 mOsm/d (about 10 mOsm/kg/d). If solute excretion in a 24-hour urine sample is greater than normal, the presence of osmotic diuresis is confirmed.

Diabetes Insipidus

DI can be classified into 2 major types: central DI and nephrogenic DI. **Central DI** is due to insufficiency or absence of endogenous ADH. **Nephrogenic DI** is due to a partial or complete unresponsiveness of the renal tubular cells to ADH. Nephrogenic DI can be caused by genetic disorders, but more commonly it is caused by various acquired conditions. Lithium, demeclocycline, and amphotericin B are well-known drugs that can cause renal concentration defects and nephrogenic DI.

Key Definitions

Central diabetes insipidus: *insufficient or absent endogenous ADH.*

Nephrogenic diabetes insipidus: *renal tubular cells partially or completely unresponsive to ADH.*

DI is diagnosed with a water deprivation study, during which the combination of high serum sodium concentration (>145 mmol/L) and low urine osmolality (<150 mOsm/kg) constitutes a positive result and is diagnostic for DI.

If a patient has both hypernatremia (>145 mmol/L) and dilute urine (<150 mOsm/kg) without receiving any aquaretic medications, those findings are sufficient to establish a diagnosis of DI. A water deprivation study is not necessary.

After a diagnosis of DI is made, intranasal or intravenous desmopressin may be administered to distinguish central DI from nephrogenic DI. Desmopressin should be administered only when the serum sodium concentration is greater than 145 mmol/L. Central DI is diagnosed if the urine osmolality increases in response to desmopressin. Nephrogenic DI is diagnosed if there is no change in urine osmolality with desmopressin.

DI-associated polyuria should be distinguished from psychogenic polydipsia. Determination of the serum sodium concentration helps with the distinction. In patients with psychogenic polydipsia, polyuria is driven by excessive water intake; thus, serum sodium concentration is typically in the lower end of the reference range (<140 mmol/L). Patients with DI, however, typically have serum sodium concentrations that are in the upper end of the reference range (>140 mmol/L) or higher.

Therapy

The same principles for correcting hyponatremia apply to correcting hypernatremia. If hypernatremia develops over the course of more than 2 days, correction of sodium concentration should be gradual (≤10 mmol/L/d).

KEY FACTS

- ✓ Hypernatremia—always associated with hyperosmolality (measurement of serum osmolality is unnecessary)
- ✓ Renal water loss—dilute urine and high urine volume (>3 L/d)
- ✓ Extrarenal water loss—maximally concentrated urine (>900 mOsm/kg)
- ✓ Drugs that can cause nephrogenic DI—lithium, demeclocycline, and amphotericin B
- ✓ Diagnosis of DI—with water deprivation study, serum sodium >145 mmol/L and urine osmolality <150 mOsm/kg

Disorders of Potassium Balance

Hypokalemia

Hypokalemia can be associated with pseudohypokalemia, transcellular shift, inadequate intake, GI loss, or renal loss. Hypokalemia (excluding pseudohypokalemia) can cause cellular hyperpolarization. Manifestations of hypokalemia include electrocardiographic (ECG) changes (blunted T wave and appearance of U wave as in Figure 54.3), muscle weakness, ileus, polyuria (functional nephrogenic DI), and, in severe cases, rhabdomyolysis and asystole.

Diagnosis

Pseudohypokalemia due to active cellular potassium uptake in the test tube (leukocytosis or leukemia) should be ruled out when appropriate. If the plasma is immediately separated from the blood sample, this error can be avoided.

Hypokalemia caused by transcellular shift is typically transient. Pertinent clinical history provides key diagnostic clues, especially for rare hereditary types of hypokalemic paralysis.

As shown in Figure 54.3, quantifying the urinary potassium level is a key step in delineating the underlying (GI or renal) causes of hypokalemia.

Therapy

Potassium repletion can be achieved with oral or intravenous supplementation. Intravenous potassium infusion is indicated for patients who have severe symptomatic hypokalemia or who lack GI access. Intravenous potassium should be given in a saline-based solution rather than a dextrose-containing solution because sugar stimulates insulin secretion, which shifts potassium intracellularly and exacerbates hypokalemia. A central line is preferred for the infusion because potassium can be corrosive to peripheral vessels. The rate of potassium infusion should not exceed 10 mmol/h.

Hyperkalemia

Hyperkalemia (Figure 54.4) can be associated with pseudohyperkalemia, excessive potassium intake, transcellular shift, and impaired secretion of renal potassium. Hyperkalemia (excluding pseudohyperkalemia) can cause cellular depolarization. Clinical manifestations include ECG changes (peaked T wave, shortened QT interval, and prolonged PR interval with widened QRS complex, as in Figure 54.4) and muscle weakness or frank paralysis. These manifestations may occur when the serum potassium concentration exceeds 6.5 to 7.0 mmol/L. Severe hyperkalemia can cause lethal cardiac arrhythmia (sine wave or complete absence of electrical activity—cardiac standstill), although a precise numerical correlation between the ECG changes and serum potassium concentrations has not been established.

Diagnosis

The first step is to rule out pseudohyperkalemia due to cell lysis during or after blood sampling from use of a small needle and inadequate technique. Use of a needle of an appropriate size and optimal technique can eliminate the problem.

Hyperkalemia caused by increased potassium intake occurs typically in patients with some degree of kidney dysfunction, and impaired kidney function is a major cause of persistent hyperkalemia. Urinary tract outlet obstruction (eg, benign prostatic hypertrophy) can lead to hyperkalemia caused by impaired collecting duct potassium excretion.

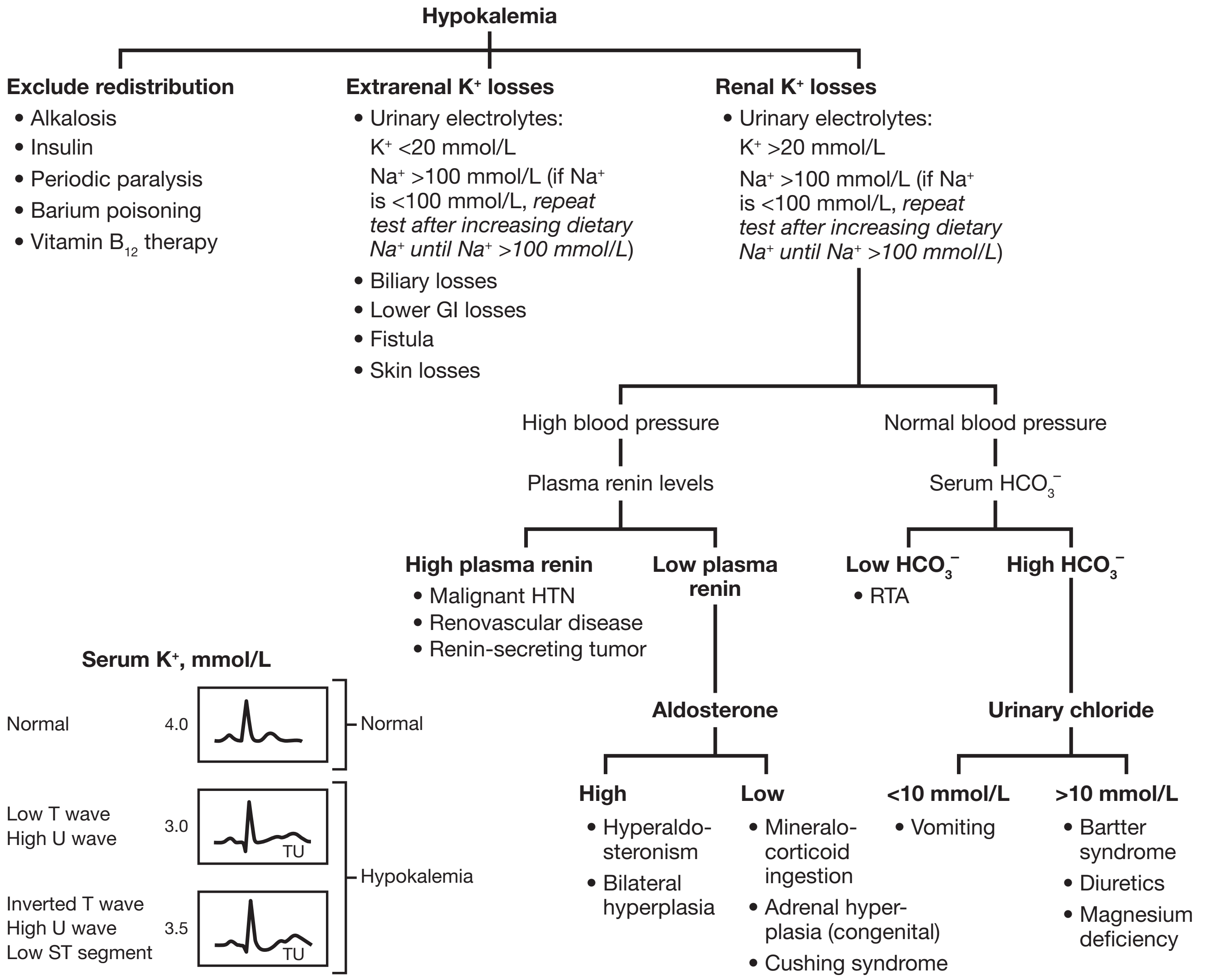
Hypokalemia
Exclude redistribution
• Alkalosis
• Insulin
• Periodic paralysis
• Barium poisoning
• Vitamin B12 therapy
Extrarenal K+ losses
• Urinary electrolytes: K+ <20 mmol/L
Na+ >100 mmol/L (if Na+ is <100 mmol/L, repeat test after increasing dietary Na+ until Na+ >100 mmol/L)
• Biliary losses
• Lower GI losses
• Fistula
• Skin losses
Renal K+ losses
• Urinary electrolytes: K+ >20 mmol/L
Na+ >100 mmol/L (if Na+ is <100 mmol/L, repeat test after increasing dietary Na+ until Na+ >100 mmol/L)
High blood pressure
Plasma renin levels
High plasma renin
• Malignant HTN
• Renovascular disease
• Renin-secreting tumor
Low plasma renin
Aldosterone
High
• Hyperaldosteronism
• Bilateral hyperplasia
Low
• Mineralocorticoid ingestion
• Adrenal hyperplasia (congenital)
• Cushing syndrome
Normal blood pressure
Serum HCO3−
Low HCO3−
• RTA
High HCO3−
Urinary chloride
<10 mmol/L
• Vomiting
>10 mmol/L
• Bartter syndrome
• Diuretics
• Magnesium deficiency
Serum K+, mmol/L
Normal
4.0
Normal
Low T wave
High U wave
3.0
TU
Inverted T wave
High U wave
Low ST segment
3.5
TU
Hypokalemia

Figure 54.3. *Diagnosis of Hypokalemia. GI indicates gastrointestinal tract; HCO_3^-, bicarbonate; HTN, hypertension; K^+, potassium; Na^+, sodium; RTA, renal tubular acidosis.*

Cellular breakdown (rhabdomyolysis and tumor lysis syndrome) can acutely release cellular potassium into the circulation. Nonorganic metabolic acidosis and hyperosmolality (hyperglycemia or administration of osmotically active solutions) can shift intracellular potassium out to the extracellular space. Other conditions that can cause hyperkalemia include hyporeninemic hypoaldosteronism and medications such as potassium-sparing diuretics, nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and heparin.

Therapy

Therapy is dictated by the severity and underlying causes of hyperkalemia. For patients with ECG changes, urgent intravenous administration of calcium is indicated to stabilize the myocardium. Simultaneously, intravenous insulin, dextrose solution (5% or 10%), and inhaled β-agonist should be administered to promote an intracellular potassium shift. If acidosis is present, sodium bicarbonate may be given to correct it. When appropriate, non–potassium-sparing diuretics and potassium-exchange resin (sodium polystyrene) may be used to promote renal and GI potassium excretion. For asymptomatic patients with mild to moderate hyperkalemia (<6 mmol/L), dietary potassium restriction, non–potassium-sparing diuretics, and potassium-exchange resin may suffice. For patients with advanced kidney failure or hyperkalemia that is refractory to conservative measures, dialysis is necessary.

Although the above measures mitigate hyperkalemia, steps should be taken to correct the underlying causes. Correcting a urinary tract obstruction can increase urinary potassium excretion. Medication-induced hyperkalemia should be corrected by adjusting the medication regimen.

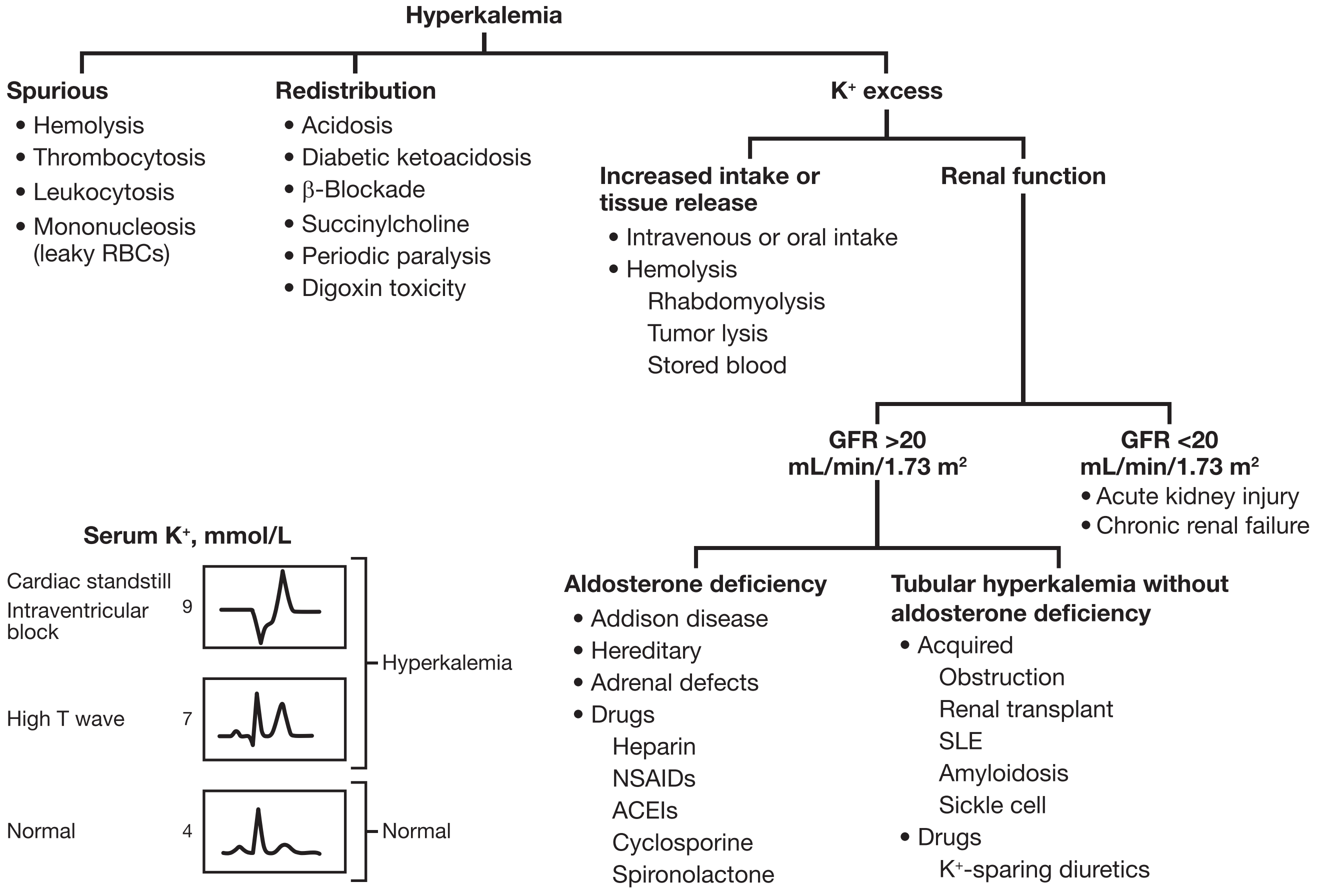
Hyperkalemia
Spurious
• Hemolysis
• Thrombocytosis
• Leukocytosis
• Mononucleosis (leaky RBCs)
Redistribution
• Acidosis
• Diabetic ketoacidosis
• β-Blockade
• Succinylcholine
• Periodic paralysis
• Digoxin toxicity
K+ excess
Increased intake or tissue release
• Intravenous or oral intake
• Hemolysis
Rhabdomyolysis
Tumor lysis
Stored blood
Renal function
GFR >20 mL/min/1.73 m2
GFR <20 mL/min/1.73 m2
• Acute kidney injury
• Chronic renal failure
Aldosterone deficiency
• Addison disease
• Hereditary
• Adrenal defects
• Drugs
Heparin
NSAIDs
ACEIs
Cyclosporine
Spironolactone
Tubular hyperkalemia without aldosterone deficiency
• Acquired
Obstruction
Renal transplant
SLE
Amyloidosis
Sickle cell
• Drugs
K+-sparing diuretics
Serum K+, mmol/L
Cardiac standstill
Intraventricular block
9
High T wave
7
Normal
4
Hyperkalemia
Normal

Figure 54.4. *Diagnosis of Hyperkalemia. ACEI indicates angiotensin-converting enzyme inhibitor; GFR, glomerular filtration rate; K+, potassium; NSAID, nonsteroidal anti-inflammatory drug; RBC, red blood cell; SLE, systemic lupus erythematosus.*

KEY FACTS

- ✓ Hypokalemia—ECG shows blunted T wave and appearance of U wave
- ✓ Therapy for hypokalemia—replete potassium before correcting acidemia
- ✓ Hyperkalemia—ECG shows peaked T wave, shortened QT interval, and prolonged PR interval with widened QRS complex
- ✓ Diagnosis of hyperkalemia—rule out pseudohyperkalemia due to cell lysis; consider kidney dysfunction, cellular breakdown, urinary tract outlet obstruction, and medications
- ✓ Drugs that can cause hyperkalemia—potassium-sparing diuretics, nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and heparin
- ✓ Therapy for severe hyperkalemia with ECG changes—urgent intravenous calcium; also, intravenous insulin and dextrose and inhaled β-agonist
- ✓ Therapy for mild to moderate hyperkalemia—dietary potassium restriction, non–potassium-sparing diuretics, and potassium-exchange resin

Disorders of Calcium Balance

Calcium (Ca^{2+}) levels are mainly regulated by vitamin D, parathyroid hormone (PTH), and calcitonin. In the circulation, roughly 50% of the calcium is bound to protein, primarily albumin. The unbound ionized form of calcium, which is approximately 45% to 50% of the calcium in circulation, is functionally active. The normal range for total serum calcium concentration in adults is 9 to 10 mg/dL.

Hypocalcemia

Diagnosis

Hypocalcemia (serum calcium concentration <8.9 mg/dL for an adult) can be caused by many conditions. In the vast majority of cases, the clinical scenario is key to an accurate diagnosis.

Patients with hypoalbuminemia from various causes can have a decreased protein-bound portion of calcium, which results in a lower total calcium concentration but a normal level of ionized calcium. For every 1-g/dL decrease in blood albumin level, the calcium concentration is decreased by approximately 0.8 mg/dL. For example, if a patient's albumin level decreases from 4.5 g/dL to 2.5 g/dL, the serum calcium concentration would be 8.0 to 8.2 mg/dL. Despite this lower level, the ionized calcium concentration should be normal because the portion that is decreased is protein bound.

Hypocalcemia can be caused by hypoparathyroidism, hypomagnesemia, vitamin D deficiency, chronic use of certain antiseizure medications such as phenytoin, and hyperphosphatemia. Hypocalcemia can also be caused by calcium redistribution, such as in 1) hungry bone syndrome, which typically develops after parathyroidectomy for hyperparathyroidism and 2) severe pancreatitis, tumor lysis syndrome, and rhabdomyolysis due to tissue calcium sequestration. Patients with hungry bone syndrome can also have development of hypomagnesemia and hypophosphatemia.

Nephrotoxic medications (eg, amphotericin and cisplatin) can cause hypocalcemia from calcium leaking out of the kidneys. Denosumab (anti-RANKL antibody) inhibits osteoclast-driven bone resorption and can result in hypocalcemia.

Therapy

Treatment of hypocalcemia depends on the cause, onset, and severity. For severe and symptomatic hypocalcemia, intravenous calcium infusion is necessary. For mild hypocalcemia, dietary optimization and oral calcium supplementation should be sufficient.

Hypercalcemia

Diagnosis

In most instances, hypercalcemia (>10.1 mg/dL) is caused by either hyperparathyroidism or a malignant process. In ambulatory settings, hypercalcemia is caused primarily by hyperparathyroidism, which is typically mild, progresses slowly, and may be asymptomatic for many years. Hypercalcemia due to cancer is usually progressive and becomes symptomatic and severe over a relatively short duration. Additional causes of hypercalcemia include vitamin A or D intoxication, granulomatous disease, hyperthyroidism, immobilization, Paget disease, familial benign hypercalcemia (low urine calcium excretion, <150 mg/d), and medications such as thiazide diuretics, lithium, and calcium-containing antacids.

Hypercalcemia can be asymptomatic or manifest as fatigue, bone and muscle aches, constipation, headaches, hypertension, irritability, decreased memory or concentration, polyuria, kidney dysfunction and stone, pancreatitis, or, rarely, coma.

Therapy

Treatment of hypercalcemia is based on the underlying cause and severity. Hypercalcemia due to hyperparathyroidism can be cured with surgery. For mild hypercalcemia due to medications such as hydrochlorothiazide and lithium, discontinuation of the medication could resolve the problem. For patients with lytic bone lesion–induced hypercalcemia, treatment is to target the cause, including treating cancer and reducing bone resorption with bisphosphonate and denosumab (targeting RANKL). Most patients with hypercalcemia have a degree of volume deficiency. Isotonic fluid administration may be necessary. Loop diuretics increase urine calcium excretion and can be used after volume repletion. For refractory cases, dialysis is effective.

Hypercalciuria

Diagnosis

Hypercalciuria is defined as urine calcium excretion >250 mg/24 h in women and >275 mg/24 h in men. Hypercalciuria is common and occurs in 5% to 10% of the general population. It is much more common in patients with calcium-containing nephrolithiasis. Chronic hypercalciuria typically occurs in patients with a history of nephrolithiasis and osteoporosis or osteopenia.

In addition to kidney stones and symptoms of reduced bone density, hypercalciuria can sometimes cause microcrystallization in the urinary tract, leading to microscopic hematuria, urinary frequency, dysuria, urgency, or a combination of these. Urinary incontinence may also result.

Diagnosis of hypercalciuria should include measurement of 24-hour urine calcium, sodium, and phosphate excretion. Measuring serum calcium, phosphate, PTH, and vitamin D levels could help with determination of the cause. A high-salt and high-protein diet, as reflected by high urinary sodium excretion (>200 mmol/24 h) and increased protein catabolic products, can promote urine calcium excretion. Causes of hypercalciuria are shown in Box 54.1.

Therapy

Dietary optimizations are helpful and should be initiated. These include appropriate dietary calcium intake, limiting dietary oxalate-containing food, and avoiding a high-salt and high-protein diet. Hypercalcemia, if present, should be treated. Increasing water intake to ensure urine output of >2.5 L/d also helps alleviate symptoms.

Disorders of Phosphate Balance

Phosphate is a major component of the skeleton and is a predominant intracellular cation. Phosphate is absorbed both by pericellular passive absorption and via its carrier protein, sodium-coupled phosphate transporter.

Box 54.1 • Causes of Hypercalciuria

Dietary

- Excessive dietary calcium intake
- Excessive vitamin D intake/intoxication
- High-salt diet
- Excessive meat intake
- Milk/alkali syndrome

Medications

- Loop diuretics
- Carbonic anhydrase inhibitors

Bone calcium mobilization

- Corticosteroid excess
- Hyperparathyroidism
- Hyperthyroidism
- Paget disease
- Bone involvement in neoplastic diseases including multiple myeloma and paraneoplastic syndrome related to osteoclastic factors

Renal calcium leak

- Idiopathic or in combination with above causes
- Medullary sponge kidney
- Renal tubular acidosis

Granulomatous diseases

- Most commonly sarcoidosis

Hypophosphatemia

Diagnosis

Hypophosphatemia (<2.5 mg/dL) can cause osteomalacia and, when severe, may cause various organ dysfunctions including respiratory insufficiency, decreased myocardial contractility, rhabdomyolysis, altered mental status, hemolysis, hepatic dysfunction, and seizure.

Common GI causes of hypophosphatemia include 1) chronic GI diseases that impair phosphate absorption, including short bowel syndrome, inflammatory bowel disease, and chronic malabsorption related to alcohol use; 2) excessive use of antacids containing aluminum, calcium, or magnesium, which bind phosphate in the gut; and 3) inadequate phosphate intake, which could contribute to or exacerbate the problems in 1) and 2), and thus worsen hypophosphatemia.

In the kidney, phosphate regulation occurs primarily at the proximal convoluted tubule. Phosphate absorption in the tubule is facilitated by sodium-phosphate cotransporters. Renal causes of hypophosphatemia include decreased PTH (PTH deters phosphate absorption) or increased vitamin D. Serum phosphate levels also regulate renal phosphate absorption through these transporters. High serum phosphate stimulates PTH secretion from parathyroid glands, which decreases renal phosphate absorption.

Acute shifts of extracellular phosphate into the intracellular space or bone can lead to hypophosphatemia. Causes of these shifts can include refeeding in the setting of chronic malnutrition, hungry bone syndrome, recovery from severe burns, prolonged intravenous nutrition with inadequate phosphate, acute respiratory alkalosis, and after treatment of diabetic ketoacidosis.

A serum phosphate level less than 2.5 mg/dL is considered hypophosphatemia. Renal phosphate loss can be diagnosed by calculating 24-hour urine fractional excretion of phosphate ($FEPO_4$). In the setting of low phosphate, $FEPO_4$ of 15% or greater strongly indicates the presence of inappropriate renal phosphate loss.

Therapy

When managing hypophosphatemia, identifying the underlying cause is critical. For instance, vitamin D deficiency and increased PTH (mostly due to primary hyperparathyroidism) should be corrected. For mild hypophosphatemia (>1.5 mg/dL), oral phosphate supplementation in divided dosages is usually effective. Severe hypophosphatemia (<1.0 mg/dL) may require intravenous phosphate supplementation.

Hyperphosphatemia

Diagnosis

Hyperphosphatemia typically occurs in patients with chronic kidney disease. If kidney function is markedly decreased, phosphate excretion could be compromised and hyperphosphatemia can develop. In patients with preserved kidney function, hyperphosphatemia can occur in the setting of hypoparathyroidism. Because phosphate is a predominantly intracellular element, tissue breakdown (eg, rhabdomyolysis and tumor lysis syndrome) can cause acute hyperphosphatemia.

Therapy

The mainstay of treatment includes dietary modification to decrease phosphate intake and initiation of phosphate binders with each meal. Hyperphosphatemia in chronic kidney disease stimulates parathyroid PTH secretion, which causes secondary hyperparathyroidism. Some vitamin D analogues can effectively inhibit PTH secretion and control the secondary hyperparathyroidism. Under such conditions, specialty nephrology and endocrinology consultations are necessary.

KEY FACTS

- ✓ Calcium levels—regulated by vitamin D, PTH, and calcitonin. In the circulation, ≈50% of the calcium is bound to protein, primarily albumin
- ✓ Blood albumin level—for every 1-g/dL decrease, the calcium concentration is decreased by ≈0.8 mg/dL

- ✓ Hypocalcemia—caused by hypoparathyroidism, hypomagnesemia, vitamin D deficiency, chronic use of antiseizure medications (eg, phenytoin), and hyperphosphatemia
- ✓ Hypercalcemia—in ambulatory settings, caused primarily by hyperparathyroidism, which is typically mild, progresses slowly, and may be asymptomatic for many years
- ✓ Hypercalciuria—urine calcium excretion >250 mg/24 h in women and >275 mg/24 h in men
- ✓ Hyperphosphatemia—typically occurs in patients with chronic kidney disease
- ✓ Hyperphosphatemia in chronic kidney disease—stimulates parathyroid PTH secretion, which causes secondary hyperparathyroidism

Disorders of Magnesium Balance

Diagnosis

Magnesium (Mg^{2+}) is abundant intracellularly, with only less than 1% located extracellularly. Of the circulating magnesium, 20% to 30% is bound to protein (mainly albumin). The unbound magnesium equilibrates with bone and intracellular magnesium and can freely filter to the kidney tubules. In adults, the ideal daily intake of magnesium is 350 to 450 mg. When magnesium is in balance, the kidneys excrete 100 mg of magnesium in the urine daily.

In hospitalized patients, hypermagnesemia (>2.3 mg/dL) and hypomagnesemia (<1.7 mg/dL) are relatively common (30% and 20% incidence, respectively). Both conditions can lead to adverse outcomes, including longer hospital stays and increased risk of death. The symptoms of dysmagnesemia can vary substantially. Patients with mild hypermagnesemia or hypomagnesemia may have no symptoms. In contrast, severe and chronic hypomagnesemia can lead to muscle weakness, paresthesia, tetany, and seizures and can potentiate cardiac arrhythmias. Severe hypermagnesemia can cause loss of deep tendon reflexes and paralysis. The causes of magnesium imbalance are varied, as shown in Box 54.2.

Therapy

Treatment of dysmagnesemia involves correcting the underlying cause(s). For severe and symptomatic hypomagnesemia, parenteral magnesium administration is indicated. Oral administration of magnesium in daily divided doses, however, is the only effective method for total body magnesium repletion. In patients with adequate kidney function, hypermagnesemia will self-correct with urine magnesium excretion. If necessary, loop diuretics can be used to enhance renal magnesium excretion. In patients with advanced kidney failure and symptomatic hypermagnesemia, intravenous calcium should be considered to temporarily stabilize the myocardium. Dialysis is the most effective and definitive treatment of hypermagnesemia in patients with kidney failure.

Box 54.2 • Causes of Magnesium Imbalance

Hypomagnesemia

Hereditary
- Maturity-onset diabetes of youth
- Gitelman syndrome
- Bartter syndrome type V

Malabsorption/chronic diarrhea

Recovery phase of obstructive uropathy and acute tubular necrosis

Hormonal deficiency
- PTH
- Insulin
- Estrogen
- Vitamin D

Medications
- Loop/thiazide diuretics
- Proton pump inhibitor
- Calcineurin inhibitors
- Cetuximab/panitumumab
- Cisplatin/carboplatin
- Aminoglycosides
- Amphotericin

Electrolyte disturbances
- Hypercalcemia
- Hyperphosphatemia
- Chronic metabolic acidosis

Hypermagnesemia

Hereditary
- Familial benign hypercalcemia (autosomal dominant inheritance)

Acquired
- Advanced kidney failure plus high magnesium intake

Magnesium-containing agents
- Laxatives/enema (milk of magnesia)
- Magnesium-containing antacids
- Magnesium infusion

Abbreviation: PTH, parathyroid hormone.

55 Renal Parenchymal Diseases

SUZANNE M. NORBY, MD; FERNANDO C. FERVENZA, MD, PHD

Tubulointerstitial Disease

Acute and chronic interstitial inflammation can result in injury to renal tubules, leading to tubular dysfunction and, chronically, tubular atrophy. Acute interstitial nephritis is discussed in Chapter 52, "Acute Kidney Injury." Causes of chronic tubulointerstitial damage include autoimmune and hereditary causes, analgesic nephropathy, uric acid, lithium, heavy metals, mercury, lead, and oxalate. Proteinuria (usually <1.5 g/1.73 m^2/24 h) and sterile pyuria may be present.

Analgesic Nephropathy

Analgesic nephropathy is a slowly progressive chronic interstitial nephritis caused by long-term consumption of mixed analgesic preparations, frequently complicated by papillary necrosis and resulting in bilateral renal atrophy. Kidney damage can develop from the use of acetaminophen in combination with aspirin and from long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs). Noncontrast computed tomography of the kidneys has become the standard method for diagnosing analgesic nephropathy. No specific treatment is available. Patients with analgesic nephropathy are at increased risk for uroepithelial tumors, particularly transitional cell carcinomas (in the renal pelvis, ureter, bladder, and proximal urethra). Tumors frequently occur simultaneously at different sites in the urinary tract, and close urologic follow-up with regular urinary cytologic examination is recommended.

Other Causes

Other causes of chronic tubulointerstitial damage include interstitial uric acid crystal formation, lithium, heavy metals, mercury, chronic lead intoxication, and oxalate deposition. Interstitial uric acid crystal formation in the renal parenchyma causes chronic uric acid nephropathy. It is associated with tophaceous gout and has limited reversibility. Lithium induces nephrogenic diabetes insipidus and microcystic changes in the renal tubules along with interstitial fibrosis. Heavy metals (eg, cadmium, certain pigments, and substances involved in manufacturing glass, plastic, metal alloys, electrical equipment, and some cigarettes) induce proximal renal tubular acidosis and tubulointerstitial nephritis. Mercury in its organic salt form can induce chronic tubulointerstitial nephritis and membranous nephropathy (MN) or acute tubular necrosis. Chronic lead intoxication can cause lead nephropathy, a form of chronic interstitial nephritis. Patients typically have hypertension, increased serum creatinine level, little or no proteinuria, bland urinary sediment, and hyperuricemia. A history of nontophaceous gout is common. Oxalate deposition from primary or secondary hyperoxaluria causes renal and extrarenal oxalate deposition. Secondary causes of oxalate deposition include enteric hyperoxaluria, ethylene glycol ingestion, methoxyflurane, high doses of ascorbic acid, and vitamin B_6 deficiency. More recently, proton pump inhibitors have been recognized as having a strong association with acute interstitial nephritis, acute kidney injury (AKI), and chronic kidney disease (CKD).

Clinical Manifestations

Clinical manifestations in patients with tubulointerstitial disease include tubular proteinuria (mainly retinol binding protein, α_1-microglobulin, or light chains), proximal tubule dysfunction, distal tubule dysfunction, medullary concentration defects, abnormal urinary sediment, azotemia, and decreased kidney function (Box 55.1).

Box 55.1 • Clinical Manifestations of Tubulointerstitial Disease

- Tubular proteinuria (<1.5-2 g/1.73 m^2/24 h; mainly retinol binding protein, α_1-microglobulin, or light chains)
- Proximal tubule dysfunction
- Distal tubule dysfunction
- Medullary concentration defects
- Abnormal urinary sediment
- Azotemia
- Decreased kidney function

Cystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease. It occurs in both males and females and is characterized by multiple bilateral renal cysts and cysts in other organs (eg, liver, spleen, and pancreas). ADPKD is most often associated with mutations in 2 genes that code for interacting proteins found in renal tubular cells and in primary cilia: The *PKD1* gene, localized on chromosome 16p, encodes polycystin 1 (85%-90% of cases), and the *PKD2* gene, localized on chromosome 4, encodes polycystin 2. Other rare mutations causing kidney and liver cysts with varying degrees of penetrance have also been discovered.

The diagnosis of ADPKD relies on the clinical and family history and imaging of the kidneys. In a patient with a family history of ADPKD, ultrasonographic criteria for diagnosis vary by age (Table 55.1). In certain settings, genetic testing is required for a definitive diagnosis.

Manifestations of kidney involvement by ADPKD can include hypertension, flank or back pain, macroscopic or microscopic hematuria, CKD, urinary tract infection, and inferior vena cava obstruction.

Extrarenal manifestations of ADPKD include polycystic liver disease (most common) and intracranial aneurysms (ICAs). The incidence of ICA is 5% to 22%, depending on whether the patient has a positive family history of ICA. Risk of rupture depends on ICA diameter (if <5 mm, risk is minimal; if >10 mm, risk is high). Screening for ICA in all patients who have ADPKD is not recommended. Instead, screening should be reserved for patients with prior known ICA, family history of ICA, or intracerebral bleeding; patients undergoing surgical procedures that may cause hemodynamic instability; and patients with occupations that may place others at risk (eg, aircraft pilots, bus drivers).

Table 55.1 • Ultrasonographic Criteria for Diagnosis of ADPKD in a Patient With a Family History of ADPKD

Age, y	Criterion
15-39	3 cysts in 1 or 2 kidneys
40-59	≥2 cysts in each kidney
≥60	≥4 cysts in each kidney

Abbreviation: ADPKD, autosomal dominant polycystic kidney disease.

Glomerular Disease

Clinical Manifestations

Clinical manifestations of glomerular injury vary. They include painless hematuria and proteinuria. *Painless hematuria* is defined as 3 or more red blood cells (RBCs) per high-power field in a freshly centrifuged urinary sediment sample. Dysmorphic RBCs or RBC casts (or both) may be present. Urine is often brown (tea- or cola-colored), rather than bright red, as a result of methemoglobin formation in acidic urine. *Proteinuria* may be nonnephrotic (0.3-3.5 g/1.73 m^2/24 h) or nephrotic (>3.5 g/1.73 m^2/24 h). Patients may report foamy urine. Proteinuria may be detected with a urine dipstick test for protein, which detects albumin. Therefore, the urine dipstick test is negative for protein if proteinuria is due to immunoglobulin light chains or tubular proteinuria.

In general, glomerular disorders are considered to be predominantly *nephritic* (characterized by hematuria and modest proteinuria) or *nephrotic* (characterized by a higher level of proteinuria), but in practice, overlap may exist (Table 55.2).

Kidney biopsy provides a definitive diagnosis and is usually indicated in the presence of active urinary sediment (dysmorphic RBCs, RBC casts, or white blood cell casts); proteinuria (usually >1 g/1.73 m^2/24 h); decreased glomerular filtration rate; AKI lasting more than 3 to 4 weeks; atypical course of diabetic nephropathy

Table 55.2 • Presentation of Glomerular Diseases in Relation to Degree of Proteinuria and Nephritic Features

Disease	Proteinuria	Nephritic Features
Minimal change nephropathy	+++++	–
Diabetic nephropathy	++++	–
Focal segmental glomerulosclerosis	++++	±
Membranous nephropathy	++++	±
IgA nephropathy	++	+++
Membranoproliferative GN	++	+++
Infection-related GN	+	++++
Rapidly progressive (crescentic) GN	+	++++
Thrombotic microangiopathy	±	±

Abbreviations: GN, glomerulonephritis; Ig, immunoglobulin; –, absent; +, present (number of symbols indicates relative degree of presence); ±, present or absent.

(DN); or suspicion of systemic diseases associated with kidney manifestations (eg, systemic lupus erythematosus [SLE], paraproteinemias and amyloidosis, systemic vasculitis, Alport syndrome, or Fabry disease). Kidney biopsy is rarely indicated for patients with small, shrunken kidneys because of an increased risk of bleeding and the low probability of providing a diagnosis. Typical characteristics of select glomerular diseases are summarized in Table 55.3.

Nephrotic Syndrome

Nephrotic syndrome is defined as a urinary protein level greater than 3.5 g/1.73 m^2/24 h along with hypoalbuminemia (<3.5 g/dL), peripheral edema (which can be prominent), hypercholesterolemia, and lipiduria in different degrees. Urinalysis shows waxy casts, free fat, oval fat bodies, and lipiduria ("Maltese crosses"). Complications of nephrotic syndrome are shown in Box 55.2.

Key Definition

Nephrotic syndrome: ***urinary protein >3.5 g/1.73 m^2/24 h, hypoalbuminemia (<3.5 g/dL), peripheral edema, hypercholesterolemia, and lipiduria.***

General management of nephrotic syndrome regardless of the cause includes managing edema with diuretics, controlling blood pressure, limiting dietary protein and sodium, treating hyperlipidemia, and using angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). The

Table 55.3 • Characteristics of Select Glomerular Diseases

Disease	Clinical Features	Characteristic Kidney Biopsy Findings	Initial Disease-Specific Treatment
Minimal change nephropathy	Abrupt onset of nephrotic syndrome with edema GFR usually preserved	LM, IF: no structural abnormalities EM: diffuse podocyte foot process effacement	ACEI or ARB Responds well to corticosteroids, although relapses are common
Focal segmental glomerulosclerosis (FSGS)	May present with full-blown nephrotic syndrome (usually primary) or asymptomatic proteinuria (secondary—see text)	LM: segmental areas of sclerosis within glomeruli EM: diffuse podocyte foot process effacement in primary FSGS; segmental in secondary FSGS	ACEI or ARB Primary: corticosteroids; may require cyclophosphamide or cyclosporine Secondary: treat underlying cause
Membranous nephropathy	Nephrotic syndrome Thrombotic complications are more common than in other disorders with nephrotic syndrome GFR usually preserved Most patients (70%-80%) are positive for anti-PLA$_2$R	LM: diffuse glomerular capillary thickening; spikes on silver stain IF: granular capillary IgG, C3 EM: subepithelial deposits	Conservative management with ACEI or ARB alone in patients at low risk for progression; corticosteroids and either a cytotoxic agent or a calcineurin inhibitor
IgA nephropathy	Various degrees of proteinuria with intermittent gross or microscopic hematuria and decreased GFR	LM: mesangial matrix expansion and mesangial cell proliferation IgA: granular mesangial IgA	ACEI or ARB High-dose corticosteroids Benefit of fish oil is controversial but probably not harmful
Membranoproliferative glomerulonephritis (MPGN)	Various degrees of proteinuria and hematuria with decreased GFR May have low C3 level and presence of C3 nephritic factor Associated with monoclonal proteins, infections, autoimmune disorders, and abnormalities of alternate complement pathway	LM: endocapillary proliferation IF: immunoglobulins and complement *or* complement alone EM: subendothelial deposits; electron-dense osmophilic deposits replacing lamina densa	Control underlying disease ACEI or ARB
Anti-GBM disease	Rapidly progressive GN; pulmonary hemorrhage may occur	LM: crescentic GN IF: linear deposition of IgG in glomerular capillary loops	High-dose corticosteroids, cyclophosphamide, plasma exchange

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; anti-PLA$_2$R, antiphospholipase A_2 receptor autoantibody; ARB, angiotensin receptor blocker; EM, electron microscopy; GBM, glomerular basement membrane; GFR, glomerular filtration rate; GN, glomerulonephritis; IF, immunofluorescence microscopy; Ig, immunoglobulin; LM, light microscopy.

Box 55.2 • Complications of Nephrotic Syndrome

Hypogammaglobulinemia—increases the risk of infection, especially cellulitis and spontaneous peritonitis

Vitamin D deficiency—due to loss of vitamin D–binding protein

Iron deficiency anemia—due to hypotransferrinemia

Thrombotic complications—due to increased levels of prothrombotic factors and decreased antithrombin III and antiplasmin

Renal vein thrombosis

use of an ACEI and an ARB together is no longer routinely recommended because it increases the incidence of AKI and hyperkalemia in some patient populations.

KEY FACTS

- ✓ Analgesic nephropathy—slowly progressive chronic interstitial nephritis, often with papillary necrosis and resulting in bilateral renal atrophy
- ✓ ADPKD—the most common hereditary renal disease
- ✓ Clinical manifestations of glomerular disease—painless hematuria and proteinuria (nonnephrotic or nephrotic), which may be accompanied by other features, including dysmorphic RBCs, RBC casts, brown urine, and foamy urine
- ✓ Management of proteinuric renal diseases—ACEI or ARB to control blood pressure and reduce proteinuria

Glomerular Diseases Usually Manifesting as Nephrotic Syndrome

Minimal Change Nephropathy

Minimal change nephropathy (MCN) is defined by the absence of structural glomerular abnormalities, except for the widespread fusion of epithelial cell foot processes seen on electron microscopy, in patients with nephrotic syndrome. It is the most common cause of nephrotic syndrome in children. The presence of nephrotic syndrome in a child with normal urinalysis results indicates MCN until proved otherwise. Among patients with nephrotic syndrome, MCN is the cause in 70% to 90% of children younger than 10 years, in 50% of adolescents and young adults, and in less than 20% of adults.

The typical presentation is abrupt onset of nephrotic syndrome. Hematuria is unusual. In adults, hypertension and AKI may be present. The pathogenesis of MCN is unknown and may be a consequence of T-lymphocyte abnormalities, with T cells producing a lymphokine that is toxic to glomerular epithelial cells. In some patients, MCN may have a secondary cause, such as viral infections, drugs, malignant processes (eg, lymphoma), or allergies.

Treatment includes high-dose corticosteroid therapy, which is continued for 4 to 8 weeks after remission is achieved. In adolescents and adults, response to therapy is high (>80%), but the response is slow and may require up to 16 weeks. Approximately 75% of patients who initially respond to corticosteroids have at least 1 relapse. Other immunosuppressive agents (eg, cyclophosphamide or cyclosporine) are used in patients with frequent relapses or corticosteroid dependence or resistance. The overall prognosis is excellent, with patients maintaining long-term kidney function. If there is no response to therapy or if progressive CKD develops, an alternative diagnosis (such as focal segmental glomerulosclerosis [FSGS]) must be considered.

Focal Segmental Glomerulosclerosis

FSGS describes a renal histologic lesion with diverse causes and pathogenicities, all of which are linked by podocyte injury and depletion. Subclasses of FSGS include primary, genetic, and secondary forms, which include maladaptive, viral, and drug-induced FSGS.

Primary FSGS typically presents as abrupt-onset nephrotic syndrome. Whereas nephrotic-range proteinuria is common in patients with secondary FSGS, full-blown nephrotic syndrome is unusual in adults with secondary FSGS.

Patients with genetic FSGS can have nonnephrotic- or nephrotic-range proteinuria or even nephrotic syndrome. Genetic FSGS results from mutations in genes encoding either critical podocyte proteins involved in slit diaphragm structure and function or the actin cytoskeleton or cell-signaling apparatus, such as *NPHS1, NPHS2, PLCE1*, and *SMARCAL1*.

Secondary causes of FSGS include drugs (eg, heroin, pamidronate, anabolic steroids, and interferon), infections (eg, HIV and parvovirus), sickle cell disease, obesity, vesicoureteral reflux, decreased renal mass (eg, unilateral renal agenesis and decreased renal mass), healed lesions of prior inflammatory disorders in glomeruli, and aging.

Treatment of primary FSGS includes prolonged (>4 months) high-dose corticosteroid therapy, which has a remission rate of 40% to 60%. For patients who do not respond to corticosteroids, alternative therapy includes other immunosuppressants (eg, cyclophosphamide, cyclosporine, or tacrolimus) either alone or in combination with corticosteroids. For patients with secondary forms of FSGS, treatment should target the underlying cause whenever possible. In all patients, treatment with an ACEI or an ARB may substantially decrease proteinuria and prolong renal survival. The prognosis is better for patients with less severe proteinuria and for those who respond to corticosteroids.

Membranous Nephropathy

MN occurs in persons of all ages and races. It is the most common cause of nephrotic syndrome in white adults and is most often diagnosed in middle age, with the incidence peaking during the fourth and fifth decades of life. The male to female ratio is 2:1. Approximately 70% of patients are positive for a circulating antiphospholipase A_2 receptor (anti-PLA_2R) autoantibody. Antibodies against thrombospondin type-1 domain-containing protein 7A (THSD7A) are present in approximately 5% of patients who are negative for anti-PLA_2R autoantibodies. The presence of anti-THSD7A antibodies has been associated with an increased risk of underlying cancer. The clinical manifestations of MN are shown in Box 55.3.

Secondary causes of MN include autoimmune diseases (eg, SLE, sarcoidosis), infections (eg, hepatitis B, hepatitis C, and syphilis), drugs (eg, NSAIDs, penicillamine, and gold), and cancers (solid tumors such as colon, breast, and lung cancer). MN is also associated with advanced age.

Initial therapy consists of general management of nephrotic syndrome, as discussed above. The probability of renal survival is more than 80% at 5 years and 60% at 15 years. With initiation of ACEI or ARB therapy, nearly 25% of patients have spontaneous complete remission, and 50% have partial remission. Traditionally, immunosuppressive therapies were considered for patients with continued nephrosis after a 6-month trial of a maximal dose of ACEI/ARB and included the use of corticosteroids in combination with a cytotoxic agent (eg, cyclophosphamide or chlorambucil), cyclosporine, tacrolimus, or rituximab. More recently, a serologic approach based on the degree of proteinuria and autoantibody levels has been proposed. Patients with persistent nephrotic syndrome unresponsive to immunosuppressive therapy are likely to have progression to end-stage renal disease (ESRD).

Nephritic Syndrome

Nephritic syndrome is defined as the presence of oliguria, edema, hypertension, proteinuria (usually <3.5 g/1.73 m^2/24 h), and active urinary sediment. General management includes sodium restriction and use of loop diuretics to decrease the risk of fluid overload and to help control hypertension.

Box 55.3 • Clinical Manifestations of Membranous Nephropathy

- High-grade proteinuria (>2.0 g/1.73 m^2/24 h in >80% of patients and >10 g/1.73 m^2/24 h in as many as 30%)
- Preserved kidney function initially in the majority of patients
- Absence of hypertension at diagnosis (>80% of patients)
- Microscopic hematuria (≈30% of patients)
- Thrombotic complications (eg, renal vein thrombosis, deep vein thrombosis, pulmonary embolism)
- Most patients (70%-80%) are positive for autoantibodies to antiphospholipase A_2 receptor (anti-PLA_2R); anti-thrombospondin type-1 domain-containing protein 7A (THSD7A) autoantibodies are present in ≈5% of patients who are anti-PLA_2R negative

KEY FACTS

✓ MCN—no structural glomerular abnormalities except for widespread fusion of epithelial cell foot processes on electron microscopy if patient has nephrotic syndrome

✓ FSGS—present in about 25% of adults with nephrotic syndrome; the most common form of idiopathic nephrotic syndrome in African Americans

✓ MN—the most common cause of nephrotic syndrome in white adults (usually occurs in middle age)

Key Definition

Nephritic syndrome: *oliguria, edema, hypertension, proteinuria (usually <3.5 g/1.73 m^2/24 h), and active urinary sediment.*

Glomerular Disease Manifesting With Nephritic Syndrome

Infection-Related Glomerulonephritis

Classic poststreptococcal glomerulonephritis (GN) develops after pharyngitis (1-3 weeks) or skin infection (2-4 weeks) due to specific (nephritogenic) strains of group A β-hemolytic streptococci. Cultures are usually negative since the infection is no longer active. Titers for antistreptolysin O and antideoxyribonuclease B may provide evidence of recent streptococcal infection. Infection-related GN may be rapidly progressive and can occur after or concomitant with other infections, such as staphylococcal, meningococcal, and pneumococcal infections; bacterial endocarditis; and infections of ventriculoatrial shunts.

A typical manifestation is the abrupt onset of nephritic syndrome. Treatment is supportive, with appropriate antibiotic therapy for persistent infections and, if applicable, for persons who are contacts (to prevent new cases). In some patients, microscopic hematuria, proteinuria, hypertension, and CKD may persist for years. These cases of atypical postinfectious GN are associated with abnormalities in the alternate pathway of complement.

Immunoglobulin A Nephropathy

Immunoglobulin (Ig) A nephropathy (IgAN) is the most common glomerulopathy worldwide, with an incidence approaching 1:100 in some countries (eg, Japan). IgAN is a mesangial proliferative GN characterized by diffuse deposition of IgA in the mesangium of glomeruli.

Most patients with IgAN are asymptomatic. This disorder may be identified if microscopic hematuria with or without proteinuria is found on routine urinalysis. In some patients, typically young adults in the second or third decade of life, IgAN may present with episodic macroscopic hematuria, often accompanying an upper respiratory tract infection ("synpharyngitic hematuria"). Proteinuria is common, but nephrotic syndrome occurs in less than 10% of all patients. Patients with nephrotic syndrome may have MCN superimposed on IgAN.

Patients who are normotensive with proteinuria less than 500 mg/1.73 m^2/24 h and normal kidney function at disease presentation usually have a good long-term prognosis. However, in 20% to 40% of patients, the disease progresses to ESRD within 10 to 25 years. Progression may be slowed by use of an ACEI or an ARB and administration of high doses of corticosteroids. The use of fish oil to prevent progression of IgAN is controversial. Persistent hematuria, proteinuria, uncontrolled hypertension, impaired kidney function at diagnosis, and fibrosis identified in kidney biopsy specimens predict a poor outcome. For patients with rapidly progressive kidney failure due to crescentic IgAN, a regimen of corticosteroids and cyclophosphamide, with the addition of plasma exchange or pulse methylprednisolone, has been tried with variable results.

Henoch-Schönlein Purpura

Henoch-Schönlein purpura is a systemic form of IgAN. It usually presents with microscopic or gross hematuria (or both), RBC casts, purpura, and abdominal pain. Generally, the prognosis is good for children and variable for adults. In patients with normal kidney function, treatment is supportive only. Patients with progressive decline in kidney function should be considered for treatment with high-dose corticosteroids with or without cytotoxic medication.

Membranoproliferative Glomerulonephritis

Membranoproliferative glomerulonephritis (MPGN) is a pattern of glomerular injury resulting from predominantly subendothelial and mesangial deposition of immune complexes or complement factors (or both) and their products, along with proliferative changes in glomeruli. MPGN can be classified according to patterns found with immunofluorescence microscopy (IF): 1) deposits of immunoglobulins and complement factors or 2) deposits of predominantly complement factors.

Immune complex–mediated MPGN shows deposition of both immunoglobulin and complement factor on IF. Immune complex–mediated MPGN usually results from chronic infection (eg, hepatitis C), cryoglobulinemia, autoimmune diseases (eg, SLE), or monoclonal gammopathies.

Complement-mediated MPGN results from dysregulation of the alternate pathway of complement and shows predominantly complement factors without substantial immunoglobulin deposition on IF. Complement-mediated MPGN can be further classified with electron microscopy into C3 glomerulonephritis (C3 GN) and dense deposit disease (DDD) (formerly known as type II MPGN). DDD can be distinguished from C3 GN on electron microscopy by the presence of electron-dense, osmophilic deposits replacing the lamina densa and producing a smooth, ribbonlike thickening.

Clinical presentation is variable and can include both nephrotic and nephritic features. In patients with cryoglobulinemic MPGN, the levels of C3, C4, and total complement (with the CH50 assay) are persistently low, which reflects activation of both complement pathways. In contrast, patients with C3 GN and DDD may have a persistently low level of C3 but a normal level of C4. Many patients have a C3 nephritic factor (an autoantibody to alternative pathway C3 convertase, which results in persistent breakdown of C3).

Treatment is aimed at resolving or controlling the underlying disease (ie, infection, SLE, or monoclonal gammopathy). The optimal treatment of idiopathic MPGN is unclear: Available data come from studies performed when the use of ACEIs and ARBs was inconsistent and currently accepted pathophysiologic processes had not yet been elucidated. Patients with normal kidney function, no active urinary sediment, and nonnephrotic-range proteinuria have favorable long-term outcomes and may be treated conservatively with ACEIs or ARBs. Follow-up is required to detect early deterioration in kidney function, which may prompt use of immunosuppressive therapy. Patients with advanced CKD and severe tubulointerstitial fibrosis on kidney biopsy are unlikely to benefit from immunosuppressive therapy.

Rapidly Progressive (Crescentic) GN

Rapidly progressive GN is defined as an acute, rapidly progressive (days to weeks or months) deterioration of kidney function associated with an active urinary sediment and a focal necrotizing crescentic GN seen on light microscopy of kidney biopsies. Oliguria is common. Three specific types of immunofluorescence patterns can be seen in kidney biopsy specimens (Figure 55.1 and Box 55.4). Pulmonary-renal syndrome occurs frequently and can be due to anti–glomerular basement membrane (GBM) disease, SLE, cryoglobulinemia, and antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) (microscopic polyangiitis, granulomatosis with polyangiitis [formerly known as Wegener granulomatosis], and eosinophilic granulomatosis with polyangiitis [formerly known as Churg-Strauss syndrome]).

Key Definition

Rapidly progressive glomerulonephritis: *acute, rapidly progressive deterioration of kidney function with active urinary sediment and focal necrotizing crescentic glomerulonephritis.*

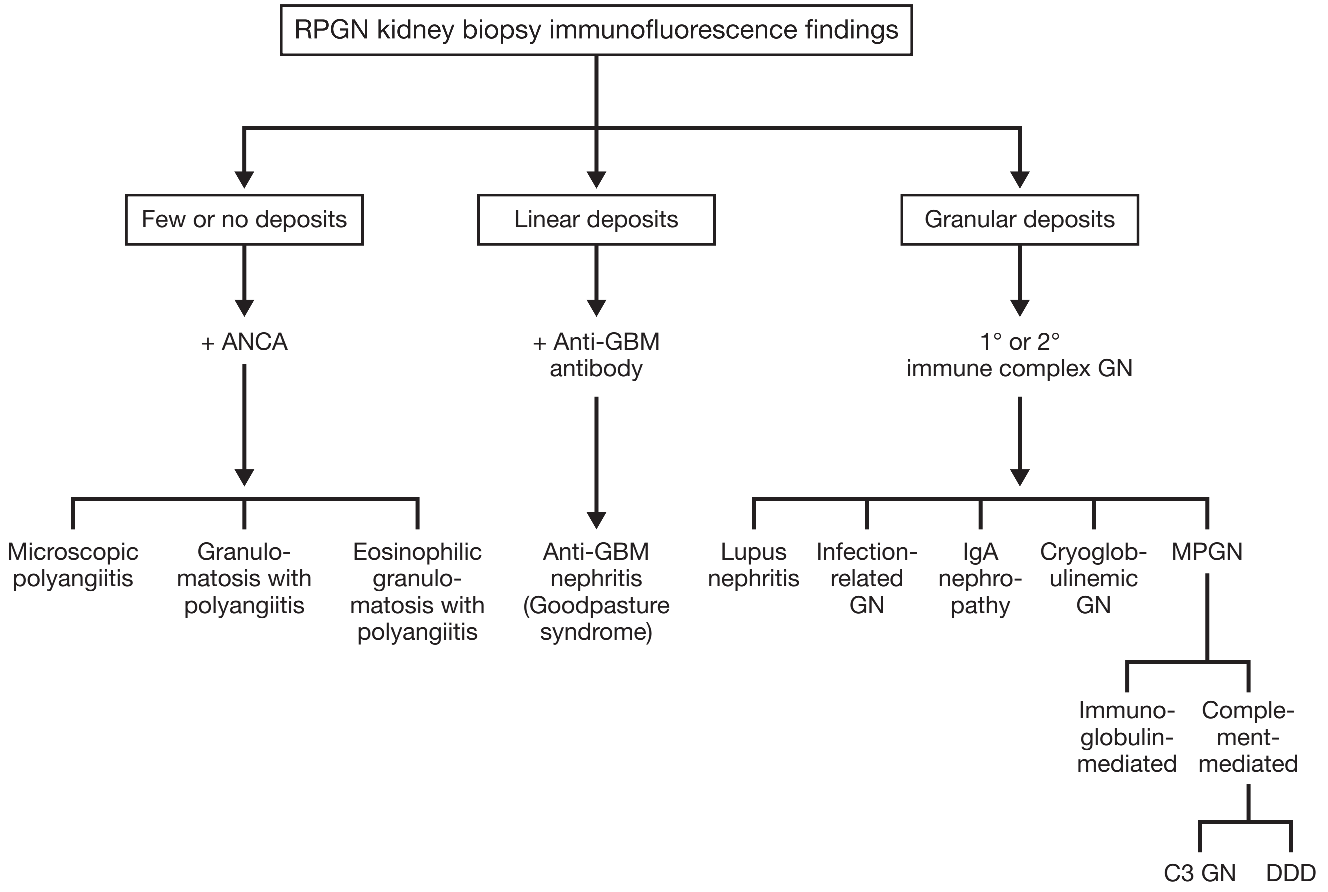
RPGN kidney biopsy immunofluorescence findings
Few or no deposits
Linear deposits
Granular deposits
+ ANCA
+ Anti-GBM antibody
1° or 2° immune complex GN
Microscopic polyangiitis
Granulomatosis with polyangiitis
Eosinophilic granulomatosis with polyangiitis
Anti-GBM nephritis (Goodpasture syndrome)
Lupus nephritis
Infection-related GN
IgA nephropathy
Cryoglobulinemic GN
MPGN
Immunoglobulin-mediated
Complement-mediated
C3 GN
DDD

Figure 55.1. *Rapidly Progressive Glomerulonephritis (RPGN). Diagnostic algorithm for glomerular disorders that may present with RPGN. Classification is based on immunofluorescence microscopy findings on kidney biopsy specimens. ANCA indicates antineutrophil cytoplasmic autoantibody; DDD, dense deposit disease; GBM, glomerular basement membrane; GN, glomerulonephritis; Ig, immunoglobulin; MPGN, membranoproliferative GN; +, presence of; 1°, primary; 2°, secondary.*

ANCA-Associated Vasculitis

AAV is characterized by inflammation and necrosis of small blood vessels of the kidney and other organs in association with autoantibodies against antigens present in lysosomal granules in the cytoplasm of neutrophils: myeloperoxidase (MPO) and proteinase 3 (PR3). AAV is the most common cause of rapidly progressive GN in patients older than 60 years and may present with a wide range of signs and symptoms (Box 55.5). The classification of AAV is outlined in Table 55.4.

Microscopic polyangiitis is a necrotizing vasculitis of small vessels (ie, capillaries, venules, and arterioles) with few or no immune deposits (pauci-immune) on IF. Necrotizing GN with crescents is common, and pulmonary capillaritis often occurs. A necrotizing arteritis involving small and medium-sized arteries can be present. Fifty percent of patients are MPO-ANCA–positive, 40% are PR3-ANCA–positive, and a few are ANCA-negative.

Granulomatosis with polyangiitis is characterized by granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small and medium-sized vessels (ie, capillaries, venules, arterioles, and arteries). Necrotizing GN is common. Most patients (75%) are PR3-ANCA–positive, and 20% are MPO-ANCA–positive.

Box 55.4 • Immunofluorescence Patterns in Rapidly Progressive GN

Type I—linear IgG deposition along GBMs: Goodpasture syndrome, anti-GBM nephritis

Type II—granular immune complexes: SLE, infection-related GN, IgA nephropathy, cryoglobulinemic GN, MPGN

Type III—pauci-immune, with negative or weak immunoglobulin deposition seen on IF: antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis

Abbreviations: GBM, glomerular basement membrane; GN, glomerulonephritis; IF, immunofluorescence microscopy; Ig, immunoglobulin; MPGN, membranoproliferative GN; SLE, systemic lupus erythematosus.

Box 55.5 • Signs and Symptoms of ANCA-Associated Vasculitis

- Cutaneous purpura, nodules, and ulcerations
- Peripheral neuropathy (mononeuritis multiplex)
- Abdominal pain and blood in stools
- Hematuria, proteinuria, and decreased kidney function
- Hemoptysis and pulmonary infiltrates or nodules
- Necrotizing (hemorrhagic) sinusitis
- Myalgias and arthralgias
- Muscle and pancreatic enzymes in blood

Abbreviation: ANCA, antineutrophil cytoplasmic autoantibody.

Eosinophilic granulomatosis with polyangiitis is characterized by peripheral blood eosinophilia, asthma or other form of atopy, an eosinophil-rich granulomatous inflammation involving the respiratory tract, and a necrotizing vasculitis affecting small and medium-sized vessels. Sixty percent of patients are MPO-ANCA–positive.

Treatment of AAV includes high-dose corticosteroids in combination with either cyclophosphamide or rituximab (anti-CD20 monoclonal antibody) until remission is achieved (3-6 months). Rituximab is equivalent to cyclophosphamide for induction therapy. For patients with pulmonary hemorrhage who require ventilatory support, plasma exchange should be added. Patients with severe kidney failure (serum creatinine level >5.5 mg/dL or receiving dialysis) can also be considered for plasma exchange. Patients who have granulomatosis with polyangiitis and are nasal carriers of *Staphylococcus aureus* benefit from long-term treatment with trimethoprim-sulfamethoxazole.

A drug-induced AAV syndrome has been reported with the use of propylthiouracil, methimazole, carbimazole, hydralazine, minocycline, levamisole-contaminated cocaine, and penicillamine. Although uncommon, drug-induced AAV should be considered in patients with vasculitis. The clinical presentation is similar to that in cases that are not drug related (Box 55.5). Most patients have MPO-ANCA, frequently in very high titers, as well as antibodies to elastase or to lactoferrin.

KEY FACTS

- ✓ Poststreptococcal GN—after pharyngitis (1-3 weeks) or skin infection (2-4 weeks) from nephritogenic group A β-hemolytic streptococci
- ✓ IgAN—most common glomerulopathy worldwide (incidence in Japan, 1:100), but most are asymptomatic
- ✓ Immune-complex–mediated MPGN—deposition of immunoglobulin and complement factor
- ✓ Complement-mediated MPGN—predominantly complement factors with relatively little immunoglobulin deposition
- ✓ Pulmonary-renal syndrome occurs with rapidly progressive GN and may be due to anti-GBM disease, AAV, SLE, or cryoglobulinemia
- ✓ AAV—inflammation and necrosis of small blood vessels in kidneys and other organs; associated with autoantibodies against MPO and PR3

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is a rare disease characterized by necrotizing inflammation of small or medium-sized arteries without GN or vasculitis in arterioles, capillaries, or venules. It affects males and females equally, with onset most frequently between the ages of 40 and 60 years. PAN is ANCA-negative. In some patients, it is associated with hepatitis B virus infection. Diagnosis is made by finding aneurysms on angiography

Table 55.4 • Classification of ANCA-Associated Vasculitis

ANCA-Associated Vasculitis	Pulmonary and Renal Features	Size of Affected Blood Vessels	Types of Antibodies, Percentage of Patients
Microscopic polyangiitis (MPA)	Pauci-immune necrotizing GN, with or without pulmonary capillaritis	Small	MPO-ANCA, 50% PR3-ANCA, 40% ANCA-negative, few patients
Granulomatosis with polyangiitis (GPA)	Granulomatous inflammation of respiratory tract with pauci-immune necrotizing vasculitis	Small and medium	PR3-ANCA, 75% MPO-ANCA, 20%
Eosinophilic granulomatosis with polyangiitis	Peripheral blood eosinophilia, asthma or atopy, eosinophil-rich granulomatous inflammation of respiratory tract with pauci-immune necrotizing vasculitis	Small and medium	MPO-ANCA, 60%

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; GN, glomerulonephritis; MPO, myeloperoxidase; PR3, proteinase 3.

or nerve biopsy. Treatment of patients who do not have evidence of hepatitis B virus infection includes high-dose corticosteroids and cyclophosphamide. Patients with hepatitis B–associated PAN should be treated with a short course of corticosteroids in combination with antiviral therapy and plasma exchange.

Anti-GBM Antibody–Mediated GN (Goodpasture Syndrome)

Anti-GBM antibody–mediated GN is a pulmonary-renal syndrome caused by circulating anti-GBM antibodies directed against the $\alpha 3$ chain of type IV collagen. Approximately 25% to 30% of patients with anti-GBM antibodies are also ANCA-positive. Pulmonary hemorrhage may be absent or not clinically apparent.

Treatment consists of high-dose corticosteroids (pulse intravenous methylprednisolone followed by oral prednisone) in combination with oral cyclophosphamide and plasma exchange. Patients who have 100% circumferential crescents on kidney biopsy and are receiving dialysis do not recover kidney function and should not be treated with the immunosuppressive regimen outlined above unless pulmonary hemorrhage is present. The prognosis depends on the percentage of circumferential crescents seen on kidney biopsy, the presence of oliguria, and the need for dialysis. Anti-GBM antibody–mediated GN rarely recurs.

Systemic Diseases Associated With Glomerular Disorders

Diabetic Nephropathy

DN is the most common cause of ESRD in the United States. It occurs in 30% to 40% of patients with type 1 diabetes mellitus (DM) and in 20% to 30% of patients with type 2 DM. In type 1 DM, the peak onset of nephropathy is 10 to 15 years after initial DM presentation. DN is unlikely to develop in patients who do not have proteinuria after 25 years of DM. The main risk factors for the development of DN are a positive family history of DN, hypertension, and poor glycemic control. The risk is greater in some ethnic groups (eg, Pima Indians and African Americans).

The initial manifestation of DN is the onset of microalbuminuria (defined as urinary albumin excretion of 20-200 mcg/min or 30-300 mg/1.73 m^2/24 h), which can evolve into overt proteinuria (>300 mg/1.73 m^2/24 h) and subsequent nephrotic-range proteinuria, although full-blown nephrotic syndrome is uncommon. After overt proteinuria develops, the progression toward ESRD is relentless, although rates of decline vary among patients (over a period of 5-15 years). The degree of proteinuria correlates approximately with the renal prognosis. Among patients with type 1 DM, there is a strong correlation between the development of nephropathy and other signs of diabetic microvascular compromise, such as diabetic retinopathy. This correlation is weaker for patients with type 2 DM; however, nephropathy develops in up to one-third of patients with type 2 DM *without* evidence of diabetic retinopathy.

The pathogenesis of DN involves increased glycosylation of proteins, with accumulation of advanced glycosylation end products that cross-link with collagen, in combination with glomerular hyperfiltration and hypertension. Kidney biopsy may not be necessary for patients with long-term DM, especially if retinopathy is present and other causes of proteinuria are excluded. Kidney biopsy is indicated if the disease has an atypical course or if progressive loss of kidney function occurs rapidly.

Progression of DN can be slowed by tight glycemic control (hemoglobin A_{1c} <7.0%) and the use of ACEIs or ARBs. Patients with ESRD due to DN are candidates for a solitary kidney or combined kidney-pancreas transplant, which affords better long-term survival and quality of life than the alternatives of hemodialysis and peritoneal dialysis.

Lupus Nephritis

Lupus nephritis (LN), one of the most serious manifestations of SLE, is observed in up to 50% of patients with SLE. Kidney involvement usually occurs early in the course of the disease and is rarely the sole manifestation of SLE.

Kidney biopsy findings are used in the classification of LN, which includes focal proliferative LN (class III); diffuse proliferative LN (class IV); and membranous LN (class V). For patients with severe LN (class III or IV), the use of a high-dose corticosteroid (depending on severity, either prednisone orally or pulsed doses of intravenous methylprednisolone) in combination with intravenous cyclophosphamide was the most effective form of therapy until more recent studies showed that mycophenolate mofetil in combination with prednisone is as effective as cyclophosphamide in combination with prednisone. Class V LN is characterized by proteinuria, weakly positive or negative antinuclear antibody results, and no RBC casts. Initial therapy is supportive, with an ACEI or an ARB used to reduce proteinuria. Immunosuppressive treatment should be considered for patients with class V LN who have nephrosis.

Cryoglobulinemic GN Associated With Hepatitis Infection

Type II or mixed essential cryoglobulins (Table 55.5) are commonly found in patients with hepatitis C virus (HCV) infection. Cryoglobulins contain HCV RNA and anti-HCV IgG, which precipitate in the glomeruli, bind complement, activate a cytokine cascade, and trigger an inflammatory response. Patients may have proteinuria, microscopic hematuria, nephrotic syndrome, or decreased kidney function. Hypertension is common and may be severe, particularly with acute nephritic syndrome. Cryoglobulinemic GN is usually associated with low levels of C3 and C4. Cryoglobulin levels correlate poorly with disease activity, and 30% to 40% of patients do not have detectable cryoglobulins. Modern antiviral treatments are effective in clearing HCV from the circulation and result in improvement

Table 55.5 • Cryoglobulins and Associated Diseases

Cryoglobulin Type	Immunoglobulin Class	Associated Diseases
I. Monoclonal immunoglobulins	M>G>A>BJP	Myeloma, Waldenström macroglobulinemia
II. Mixed cryoglobulins with monoclonal immunoglobulins	M/G>>G/G	Sjögren syndrome, Waldenström macroglobulinemia, lymphoma, essential cryoglobulinemia
III. Mixed polyclonal immunoglobulins	M/G	Infection, SLE, vasculitis, neoplasia, essential cryoglobulinemia

Abbreviations: BJP, Bence Jones protein; SLE, systemic lupus erythematosus.

of proteinuria and kidney function. Relapses after discontinuation of antiviral therapy are common. For patients with acute nephritis, treatment with prednisone and cytotoxic agents is indicated, with the addition of plasmapheresis, depending on the severity. The renal prognosis is usually favorable.

KEY FACTS

- ✓ PAN—rare; necrotizing inflammation of small or medium-sized arteries without GN or vasculitis in arterioles, capillaries, or venules
- ✓ Anti-GBM disease—a pulmonary-renal syndrome caused by circulating anti-GBM antibodies directed against the $\alpha3$ chain of type IV collagen
- ✓ DN—the most common cause of ESRD in the United States
- ✓ Initial manifestation of DN—microalbuminuria (urinary albumin excretion, 20-200 mcg/min or 30-300 mg/1.73 m^2/24 h)

HIV–Associated Nephropathy

Human immunodeficiency virus (HIV)-associated nephropathy is characterized by progressive CKD in patients with nephrotic-range proteinuria (frequently massive) but often little edema. Ultrasonography shows large, echogenic kidneys. Kidney biopsy shows a collapsing form of FSGS. HIV-associated nephropathy is typically seen in African Americans. Treatment includes the use of highly active antiretroviral therapy, treatment of underlying infections, and an ACEI to reduce proteinuria.

Other types of kidney disease can be encountered in HIV-infected patients. These include IgAN, MPGN, MCN, MN, infection-related GN, thrombotic microangiopathy (TMA), and a lupuslike immune complex–mediated GN. Intratubular obstruction can result from crystal precipitation after the administration of sulfadiazine or intravenous acyclovir. Renal calculi or nephropathy (or both) can occur after administration of indinavir.

Paraproteinemia-Associated Kidney Diseases

Multiple Myeloma

Multiple myeloma may have renal manifestations such as AKI or progressive CKD, which can occur at any time during the course of the disease. Other renal manifestations include pseudohyponatremia, low anion gap, and type 2 (proximal) renal tubular acidosis with Fanconi syndrome. Virtually all patients with multiple myeloma have monoclonal immunoglobulins or light chains in the serum or urine (or in both). AKI occurs as a result of intraluminal precipitation of proteinaceous casts (cast nephropathy) and the resulting interstitial inflammatory reaction (myeloma kidney). Intratubular cast formation is facilitated by increased urinary concentrations of calcium, sodium, and chloride (eg, after the use of a loop diuretic); conditions that reduce flow rates (eg, intravascular depletion and the use of NSAIDs); and use of radiocontrast agents.

Treatment of cast nephropathy includes vigorous hydration with normal saline, correction of hypercalcemia, avoidance of nephrotoxic or precipitating agents, alkalization of the urine to maintain a pH greater than 7 (possibly beneficial in some patients), and consideration of plasmapheresis (which quickly removes light chains from the circulation) for patients with AKI and high serum levels of free light chains or hyperviscosity syndrome.

Amyloidosis

Amyloidosis may be primary (AL amyloidosis), secondary (AA amyloidosis), or familial. AL amyloidosis is characterized by systemic extracellular deposition of antiparallel, β-pleated sheet, nonbranching, 8- to 12-nm fibrils that stain positive with Congo red (showing green birefringence with polarized light) or thioflavin T.

Patients with primary (AL) amyloidosis are typically older than 50 years, and the kidneys are affected in 50% of patients. New advances in treatment of amyloidosis, including stem cell transplant, have greatly improved the previously dismal prognosis.

Secondary (AA) amyloidosis is most common in patients who have rheumatoid arthritis, inflammatory bowel disease, chronic infection, or genetic mutations (eg, familial Mediterranean fever) and in persons who subcutaneously inject illicit drugs such as heroin. The treatment of AA amyloidosis is directed at the underlying inflammatory process.

Light Chain Deposition Disease

Light chain deposition disease is characterized by immunoglobulin light chain deposition along the GBM. It is strongly associated with the development of myeloma, lymphoma, and Waldenström macroglobulinemia. Kidney involvement is manifested by proteinuria, nephrotic syndrome, and decreased kidney function. As in amyloidosis and multiple myeloma, treatment can lead to stabilization or improved kidney function in some patients.

Thrombotic Microangiopathies

Different types of TMA are characterized by decreased kidney function, along with microangiopathic hemolytic anemia and thrombocytopenia. The pathogenesis of various disorders that present as TMA is becoming clearer, and the terminology is evolving. Diagnostic features include anemia with schistocytes on peripheral blood smear, high reticulocyte count, increased levels of indirect bilirubin and lactate dehydrogenase, decreased haptoglobin level, and presence of urinary hemoglobin without RBCs on microscopy. Making a diagnostic distinction between hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) can be difficult. Traditionally, HUS is more commonly associated with AKI, and patients with TTP typically have fever, neurologic signs, and purpura.

Hemolytic Uremic Syndrome

The sporadic or diarrhea-associated form of HUS (D+HUS) is strongly linked to ingestion of meat or other foods contaminated with *Escherichia coli* O157:H7, which produces a Shigalike toxin that binds to a glycolipid receptor on renal endothelial cells and triggers endothelial damage. The treatment is supportive; antibiotics should not be used because they can cause additional release of toxins. Children with D+HUS have a good prognosis (90% recover kidney function), but older patients have an increased mortality rate and unfavorable long-term renal survival.

Thrombotic Thrombocytopenic Purpura

Typically, fluctuating neurologic signs and symptoms along with purpura are more commonly associated with TTP. TTP may result from an autoantibody to the von Willebrand factor–cleaving protease ADAMTS13 (acute form) or from deficiency of ADAMTS13 (chronic-relapsing form). An ADAMTS13 activity measurement greater than 5% excludes severe ADAMTS13 deficiency (congenital or acquired TTP). In addition, TTP can occur in association with certain drugs (eg, cocaine, quinidine, ticlopidine, oral contraceptives, cyclosporine, tacrolimus, mitomycin C, bleomycin, and vascular endothelial growth factor inhibitors), HIV infection, cancers, radiotherapy, SLE, antiphospholipid antibody syndrome, and scleroderma renal crisis. In general, treatment of TTP consists of plasma exchange, although scleroderma renal crisis is treated with ACEIs.

Complement-Mediated TMA

Atypical HUS is now recognized to be a complement-mediated form of TMA, resulting from various inherited and acquired abnormalities of the proteins involved in the alternate pathway of complement activation. It may be acquired (formation of antibody to Factor H) or genetic (mutations in the genes coding for C3, CD46, and complement factors H, I, and B).

Eculizumab, an inhibitor of the C5 complement component that blocks formation of the C5b-9 membrane attack complex, has been approved for the treatment of atypical HUS. Eculizumab or plasma exchange (or both) may also be considered in the treatment of children with D+HUS and severe central nervous system involvement (eg, seizures or coma).

Diseases With Intrinsic GBM Abnormalities

Alport Syndrome

Alport syndrome is characterized by a progressive nephritis manifested by persistent or intermittent hematuria and proteinuria that increases with age. It is frequently associated with sensorineural hearing loss and ocular abnormalities. In virtually all male patients, the syndrome progresses to ESRD, often by age 16 to 35 years. This disorder is usually mild in heterozygous females, although ESRD develops in some women, usually after age 50 years. The rate of progression to ESRD is fairly constant among affected males within individual families but varies markedly from family to family.

The diagnostic abnormality is the absence of α3, α4, and α5 chains of type IV collagen from the GBM and distal tubular basement membrane. This abnormality occurs only in patients with Alport syndrome. More than 50% of patients have a mutation in the gene (*COL4A5*) that codes for the α5 chain of type IV collagen, α5(IV). It is X-linked in at least 80% of the patients. Additionally, autosomal recessive and autosomal dominant patterns of inheritance have been described. In families with a previously defined mutation, molecular diagnosis of affected males or gene-carrying females is possible. For families in which mutations have not been defined, genetic linkage analysis can determine whether an at-risk person carries the mutant gene, provided that at least 2 other affected members are available for testing.

No specific treatment is available. Tight control of blood pressure and moderate dietary protein restriction are recommended, and ACEI use can slow the progression of CKD. Renal replacement therapy is eventually required. If the defect is in the α5(IV) chain, these patients are a phenotypic knockout for the α3(IV) chain. Thus, patients with Alport syndrome who receive a kidney transplant have a 5% to 10% risk of Goodpasture syndrome developing because of the presence of the α3(IV) chain (the location of the "Goodpasture antigen") in the transplanted kidney.

KEY FACTS

- ✓ HIV-associated nephropathy—progressive renal insufficiency and proteinuria (frequently massive) but often little edema
- ✓ Thrombotic microangiopathies (eg, HUS and TTP)—microangiopathic hemolytic anemia, thrombocytopenia, and renal failure
- ✓ Alport syndrome—progressive nephritis with persistent or intermittent hematuria and proteinuria (increases with age); frequently associated with sensorineural hearing loss and ocular abnormalities

Thin Basement Membrane Nephropathy

Thin basement membrane nephropathy (TBMN), sometimes referred to as benign familial hematuria, is a relatively common condition characterized by *isolated* glomerular hematuria (proteinuria is usually absent) associated with the kidney biopsy finding of an excessively thin GBM (typically <250 nm in adults). Although TBMN is transmitted in a dominant fashion, patients with TBMN can be considered carriers of the autosomal recessive Alport syndrome because mutations (homozygous or compound heterozygous) in both alleles of *COL4A3* or *COL4A4* cause autosomal recessive Alport syndrome.

The clinical presentation includes persistent or intermittent hematuria that is first detected in childhood or during a routine urinalysis and is sometimes not manifested until adulthood. Macroscopic hematuria is not uncommon and may occur in association with an upper respiratory tract infection. Blood pressure is typically normal. When TBMN is first detected in young adults, 60% have proteinuria less than 500 mg/1.73 m^2/24 h. In contrast to patients with Alport syndrome, patients with TBMN do not have hearing loss, ocular abnormalities, or a strong family history of ESRD. The diagnosis of TBMN requires a kidney biopsy and electron microscopy with measurement of GBM thickness. For most patients who have isolated hematuria and a negative family history of ESRD, the condition is benign, requires no specific treatment, and carries an excellent long-term prognosis. In some patients, progressive proteinuria and CKD may develop and can eventually result in ESRD. TBMN has been reported to occur in association with other glomerular diseases.

VIII

Questions and Answers

Questions

Multiple Choice (Choose the best answer)

VIII.1. A 58-year-old woman with a history of type 2 diabetes mellitus and chronic kidney dysfunction was seen at a regular follow-up visit. Her examination showed blood pressure 148/90 mm Hg, pulse rate 65 beats/min, and respiratory rate 14 breaths/min. Other findings were benign except for trace lower extremity edema. She had been taking insulin, baby aspirin (81 mg, 1 tablet once daily), and amlodipine (10 mg once daily). Her laboratory studies showed the following: $[\text{Na}^+]$ 135 mmol/L, $[\text{K}^+]$ 5.1 mmol/L, $[\text{Cl}^-]$ 106 mmol/L, $[\text{HCO}_3^-]$ 17 mmol/L, blood urea nitrogen 30 mg/dL, and creatinine 1.7 mg/dL. Arterial blood gas evaluation showed pH 7.32 and $P\text{co}_2$ 32 mm Hg. What is the most likely diagnosis to account for her acid-base status?

a. Type 1 distal renal tubular acidosis
b. Type 2 proximal tubular acidosis
c. Respiratory alkalosis
d. Type 4 renal tubular acidosis

VIII.2. A 24-year-old man was admitted after a motor vehicle accident. He sustained multiple rib fractures, and flail chest developed. He received narcotics for pain control. On examination, he appeared sleepy but arousable. His blood pressure was 130/86 mm Hg, pulse rate was 100 beats/min, respiratory rate was 16 breaths/min, and O_2 saturation was 99% on room air. Blood chemistry values were as follows: $[\text{Na}^+]$ 135 mmol/L, $[\text{K}^+]$ 4.8 mmol/L, $[\text{Cl}^-]$ 100 mmol/L, $[\text{HCO}_3^-]$ 25 mmol/L, blood urea nitrogen 24 mg/dL, creatinine 1.0 mg/dL, blood pH 7.32, $P\text{co}_2$ 49 mm Hg, and $P\text{o}_2$ 90 mm Hg. What is the most appropriate diagnosis?

a. Chronic respiratory acidosis superimposed with metabolic alkalosis
b. Acute respiratory acidosis
c. Acute respiratory alkalosis superimposed with metabolic acidosis
d. Chronic respiratory alkalosis

VIII.3. A 34-year-old woman with a history of low back pain and some history of alcohol abuse recently underwent back surgery. Post surgery, she was taking acetaminophen and ibuprofen for pain. She sought care for reported weakness. She appeared malnourished. Her blood pressure was 98/58 mm Hg, pulse rate was 62 beats/min, and body mass index was 19 kg/m^2. Examination findings were benign. There was no dependent edema. Laboratory studies showed $[\text{Na}^+]$ 136 mmol/L, $[\text{K}^+]$ 3.8 mmol/L, $[\text{Cl}^-]$ 100 mmol/L, $[\text{HCO}_3^-]$ 14 mmol/L, blood urea nitrogen 12 mg/dL, and creatinine 0.5 mg/dL. Arterial blood gas evaluation showed blood pH 7.32 and $P\text{co}_2$ 29 mm Hg. Further examination of her blood lactate, ethanol, methanol, ethylene glycol, and salicylate levels were all within reference ranges. Her blood acetaminophen level was nondetectable. What is the best next step in management?

a. Blood D-lactate measurement
b. Blood or urine oxoproline measurement
c. Blood propylene measurement
d. Urine drug screen

VIII.4. A 59-year-old man with chronic obstructive pulmonary disease (COPD), congestive heart failure, obesity (body mass index, 38.2 kg/m^2), and an ileal conduit is admitted for total knee replacement surgery. His current medications are acetaminophen, albuterol/ipratropium (inhaled), atorvastatin, and metoprolol. He receives acetaminophen and oxycodone for postoperative pain control. On postoperative day 2, the patient is somnolent and difficult to arouse. On examination, his blood pressure is 136/86 mm Hg, pulse 90 beats/min, respirations 8 breaths/min, temperature 37.5°C, and $S\text{po}_2$ 91% on 6 L O_2. He is unresponsive to verbal stimuli. Heart examination shows a regular rate and rhythm, lung examination reveals decreased basilar breath sounds, bowel sounds are present and his abdomen is soft and nondistended, his extremities show no edema, and no rashes are present. Standard laboratory testing is ordered urgently. Chest radiography shows new, small, bilateral pleural effusions. Additional findings are shown in Table VIII.Q4.

Table VIII.Q4. ●

Measure	Value
White blood cells	8.0 × 10^9/L
Platelets	154 × 10^9/L
Hemoglobin	14.3 g/dL
Sodium	140 mmol/L
Potassium	4.6 mmol/L
Chloride	101 mmol/L
Bicarbonate	29 mmol/L
Blood urea nitrogen	34 mg/dL
Creatinine	1.5 mg/dL
Glucose	131 mg/dL
Arterial blood gases	
pH	7.24
P_{O_2}	96 mm Hg
P_{CO_2}	81 mm Hg

Abbreviations: P_{CO_2}, partial pressure of carbon dioxide; P_{O_2}, partial pressure of oxygen.

What is the most likely diagnosis in this patient?

a. Normal anion gap metabolic acidosis
b. Chronic respiratory acidosis
c. Acute respiratory acidosis
d. Mixed acute and chronic respiratory acidosis

VIII.5. A 46-year-old woman is evaluated in the hospital 8 hours after a witnessed seizure. Urine output over the past 2 hours was 60 mL. She reports diffuse myalgias. Her medical history includes obesity and depression. Before admission, her only medication was paroxetine. Levetiracetam was initiated during this hospitalization. Vital signs are temperature 37.6°C, blood pressure 154/92 mm Hg, and pulse 88 beats/min. On physical examination, oral mucous membranes are moist and skin turgor is normal. Examination of the heart and lungs shows normal findings. Peripheral edema is absent.

Laboratory studies show sodium 141 mEq/L, potassium 5.4 mEq/L, chloride 106 mEq/L, bicarbonate 21 mEq/L, creatinine 2.1 mg/dL, blood urea nitrogen (BUN) 26 g/dL, calcium 8.3 mg/dL, phosphorus 6.2 mg/dL, albumin 4.2 mg/dL, aspartate aminotransferase 102 U/L, and creatine kinase 18,400 U/L. Urinalysis shows specific gravity 1.012, 3+ blood, 2+ protein, and negative leukocyte esterase and nitrites. Urine microscopy shows 4 to 10 renal epithelial cells per high-power field and granular casts. Electrocardiography findings are normal. Which of the following is the most appropriate next step in management?

a. Intravenous (IV) 0.9 N saline at 250 mL/h
b. Sodium bicarbonate 50 mEq IV
c. Furosemide 40 mg IV
d. Calcium gluconate 1 g IV

VIII.6. A 73-year-old man is seen in the clinic for a reassessment after hospital dismissal 2 weeks earlier. During an evaluation for exertional dyspnea before the hospitalization, exercise stress echocardiography demonstrated inducible hypokinesis of the anterior wall with stress, and the left ventricular ejection fraction decreased from 60% at rest to 45% at peak stress. There was no significant valvular disease. He underwent coronary arteriography with placement of a drug-eluting stent in the left anterior descending artery and was discharged the following day with no apparent complications. At the current evaluation, he feels well with no recurrence of exertional dyspnea. His medical history includes type 2 diabetes mellitus for 6 years and hypertension and hyperlipidemia for 20 years. His medications are lisinopril 20 mg daily, atenolol 50 mg daily, atorvastatin 40 mg daily, aspirin 81 mg daily, and insulin. Clopidogrel 75 mg daily was added during the hospitalization; no other medication changes were made. Vital signs are blood pressure 128/74 mm Hg, pulse 66 beats/min, respiratory rate 14 breaths/min, weight 102 kg, and temperature 37°C. Physical examination discloses normal mucous membranes, normal heart, lungs, and abdomen, faded ecchymosis at the right groin arterial puncture site, and faint livedo reticularis on both feet. Peripheral edema is absent.

Laboratory studies are shown in Table VIII.Q6.

Table VIII.Q6. ●

Measure	2 Weeks Ago	Today
Creatinine, mg/dL	1.2	2.2
Estimated glomerular filtration rate, mL/min/1.73 m^2	69	29
Blood urea nitrogen, mg/dL	14	26

Urinalysis shows trace protein and no hemoglobin. Urine microscopy shows 1 to 3 leukocytes per high-power field. The urine protein/creatinine ratio is 143 mg/g. Renal ultrasonography findings are within normal limits. Which is the most likely diagnosis?

a. Cardiorenal syndrome
b. Renal atheroemboli
c. Hemodynamic effect of lisinopril
d. Contrast-associated acute kidney injury (AKI)

VIII.7. A 62-year-old woman is admitted to the hospital with worsening ascites over the past 2 weeks. Her medical history includes chronic hepatitis C infection with cirrhosis and portal hypertension. She had been taking spironolactone 50 mg daily, and furosemide 40 mg daily was added 10 days ago. She was taking no other medications. Despite the addition of furosemide, her abdominal girth continued to increase. She also had noticed intermittent melena. Vital signs are blood pressure 84/68 mm Hg, pulse 94 beats/min, respiratory rate 18 breaths/min, temperature 37.2°C, and weight 78 kg. Physical examination discloses moist oral mucous membranes, regular cardiac rate and rhythm with a grade II/VI holosystolic murmur along the left sternal border, clear lungs, and a prominently distended, soft abdomen with fluid wave present. Several spider veins are noted. There is no peripheral edema.

Laboratory studies are shown in Table VIII.Q7.

Table VIII.Q7. ●

Measure	6 Weeks Ago	Yesterday
Hemoglobin, g/dL	11.6	9.2
Leukocytes, ×10^9/L	5.6	7.9
Platelets, ×10^9/L	126	119
International normalized ratio	1.4	1.8
Sodium, mEq/L	135	130
Potassium, mEq/L	4.9	5.2
Chloride, mEq/L	100	97
Bicarbonate, mEq/L	25	21
Creatinine (SCr), mg/dL	0.7	1.6
Estimated glomerular filtration rate, mL/min/1.73 m^2	> 60	40
Blood urea nitrogen, mg/dL	10	18

The urine sodium level is less than 10 mEq/L. Urinalysis shows trace protein and 1+ hemoglobin. Urine microscopy shows 1 to 3 red blood cells (RBCs) and 1 to 3 white blood cells per high-power field. Abdominal ultrasonography shows increased hepatic echogenicity, splenomegaly, and normal kidneys, in addition to ascites. Spironolactone and furosemide are discontinued, and 300 mL 25% albumin is administered intravenously daily on 2 successive days. Urine output yesterday was 740 mL. Today, the SCr value is 1.7 mg/dL. What is the most likely diagnosis?

a. Cryoglobulinemia
b. Immune complex–mediated glomerulonephritis
c. Interstitial nephritis
d. Hepatorenal syndrome (HRS)

VIII.8. A 66-year-old man has a history of diabetic nephropathy and hyperlipidemia. He has been treated with simvastatin for the past 7 years without complication. He now has end-stage renal disease and has started hemodialysis. How should his hyperlipidemia be managed now that he has started dialysis?

a. Check cholesterol levels and continue treatment if the low-density lipoprotein (LDL) value is >100 mg/dL.
b. Continue current therapy if there are no adverse effects.
c. Discontinue simvastatin.
d. Discontinue simvastatin and initiate ezetimibe.

VIII.9. A 62-year-old woman has a history of end-stage renal disease secondary to polycystic kidney disease. She recently had a kidney transplant. Her laboratory test results show hyperkalemia (potassium, 6.0 mg/dL). Which of her following medications is least likely to be associated with hyperkalemia?

a. Proton pump inhibitor
b. Trimethoprim-sulfamethoxazole
c. Calcineurin inhibitor
d. Metoprolol

VIII.10. A patient has stage 4 chronic kidney disease (CKD) and anemia, with a hemoglobin value of 10.0 mg/dL. What laboratory findings are expected in anemia of CKD?

a. Microcytosis with high transferrin level, low transferrin saturation, and low ferritin level
b. Normocytic anemia with low transferrin level and low transferrin saturation
c. Macrocytosis with low transferrin level and low transferrin saturation
d. Normocytic anemia with low transferrin level, high transferrin saturation, and high ferritin level

VIII.11. A 68-year-old man with no significant medical history sought care for new-onset cough of 3 months' duration. He reported some weakness and loss of balance. Evaluation showed normal vital signs, and chest computed tomography showed a hilar mass lesion. Laboratory studies showed the following serum values: sodium 122 mmol/L, potassium 3.6 mmol/L, chloride 91 mmol/L, bicarbonate 24 mmol/L, blood urea nitrogen 20 mg/dL, and creatinine 0.9 mg/dL. Urinalysis showed osmolality of 560 mOsm/kg. Microscopy findings were within normal range. The patient formerly was a cigarette smoker (30 pack-years) and quit smoking 10 years ago. He also reports drinking beer several times per week. What is the most likely cause of the patient's hyponatremia?

a. Reduced solute intake
b. Syndrome of inappropriate antidiuretic hormone (SIADH)
c. Undiagnosed hepatic failure and cirrhosis
d. Beer potomania

VIII.12. A 42-year-old woman is brought to the emergency department unresponsive and diaphoretic. She has no other localizing signs on examination. She has a history of depression, insulin-dependent diabetes mellitus, and chronic pain thought to be a result of a motor vehicle accident. She has no history of previous electrolyte disorders. Her blood pressure is 102/66 mm Hg, pulse 110 beats/min, respiration rate 17 breaths/min, and temperature 36.0°C. Laboratory findings are shown in Table VIII.Q12.

Table VIII.Q12.

Measure	Value
White blood cells	7.8 × 10^9/L
Platelets	318 × 10^9/L
Hemoglobin	14.9 g/dL
Sodium	141 mmol/L
Potassium	2.1 mmol/L
Chloride	108 mmol/L
Bicarbonate	24 mmol/L
Blood urea nitrogen	21 mg/dL
Creatinine	1.1 mg/dL
Glucose	34 mg/dL
Arterial blood gases	
pH	7.39
Po_2	67 mm Hg
Pco_2	39 mm Hg

What is the most likely diagnosis in this case?

a. Renal tubular acidosis
b. Hypokalemia periodic paralysis
c. Insulin overdose
d. Hyperaldosteronism (Conn syndrome)

VIII.13. A 70-year-old woman with a history of bipolar disorder, hypothyroidism, and carotid endarterectomy is an inpatient after hip replacement. Her current medications are aspirin, sodium citrate, levothyroxine, lithium, lorazepam, pentoxifylline, and simvastatin. On postoperative day 4 she has mental status change, polyuria, and hypernatremia. Her physical examination findings are body mass index 20 kg/m^2, blood pressure 116/78 mm Hg, pulse 68 beats/min, and respiration rate 18 breaths/min. She appears somnolent and is slow to respond to questions. Her lung fields are clear and she has no peripheral edema. Laboratory findings are shown in Table VIII.Q13 (next page). What is the most likely cause of her hypernatremia?

a. Nephrogenic diabetes insipidus
b. Osmotic diuresis
c. Accidental diuretic administration
d. Insufficient water intake

VIII.14. A 62-year-old man is seen in the clinic for a periodic health evaluation. He feels well and has no concerns. His medical history includes type 2 diabetes mellitus for 8 years, hypertension, hyperlipidemia, stage 3a chronic kidney disease, gastroesophageal reflux disease, and benign prostatic hypertrophy. Medications are metformin 1,000 mg twice daily, losartan 100 mg daily, amlodipine 5 mg daily, atorvastatin 20 mg daily, pantoprazole 40 mg daily, and tamsulosin 0.4 mg daily. Vital signs are temperature 37.1°C, blood pressure 128/82 mm Hg, pulse 78 beats/min, and weight 98 kg. Physical examination shows

Table VIII.Q13. •

Measure	Value
Blood values	
White blood cells	8.3 × 10^9/L
Platelets	235 × 10^9/L
Hemoglobin	14.3 g/dL
Hematocrit	44.1%
Sodium	161 mmol/L
Potassium	4.2 mmol/L
Chloride	130 mmol/L
Bicarbonate	24 mmol/L
Blood urea nitrogen	46 mg/dL
Creatinine	1.7 mg/dL
Glucose	139 mg/dL
Calcium	10.5 mg/dL
Phosphorus	5.0 mg/dL
Parathyroid hormone	88 pg/mL
Urine values	
Osmolality	98 mOsm/kg
pH	6.7
Glucose	<2 mg/dL
Predicted 24-h protein	145 mg (range, 36-586 mg)
Microscopy	White blood cells 1-3; bacteria

truncal obesity and a symmetrically enlarged prostate gland with no nodules and is otherwise within normal limits. Laboratory studies are shown in Table VIII.Q14.

On the basis of these results, metformin is discontinued and insulin is initiated. On additional testing, urinalysis shows 2+ protein; urine microscopy shows 21 to 30 white blood cells per high-power field and occasional renal epithelial cells; urine Gram stain is negative; 24-hour urine total protein is 1.2 g; serum and urine monoclonal protein studies and serum free light chains are within normal limits; postvoid residual urine measurement by ultrasonography is 32 mL; and ultrasonography of the kidneys shows echogenic kidneys with no hydronephrosis, left kidney, 12.2 cm, and right kidney, 12.6 cm. Which of the following is the most appropriate next step in management?

Table VIII.Q14. •

Measure	6 Months Ago	Currently
Hemoglobin, g/dL	13.6	13.8
Leukocytes, ×10^9/L	6.6	7.9
Platelets, ×10^9/L	326	279
Sodium, mEq/L	135	139
Potassium, mEq/L	4.3	4.8
Chloride, mEq/L	101	104
Bicarbonate, mEq/L	24	22
Creatinine, mg/dL	1.4	2.3
Estimated glomerular filtration rate, mL/min/1.73 m^2	53	37
Blood urea nitrogen, mg/dL	13	35
Fasting glucose, mg/dL	124	136
Hemoglobin A_{1c}, %	6.8	7.2
Urine microalbumin, mg/g	293	316

a. Kidney biopsy
b. Computed tomography (CT) of the abdomen and pelvis without contrast
c. Discontinuation of lisinopril
d. Doppler ultrasonography of the renal arteries

VIII.15. A 34-year-old woman is seen in the clinic to discuss results of a kidney biopsy performed 2 days ago after evaluation of a 3-week history of tea-colored urine, lower extremity edema, and facial rash. Her only medication was atorvastatin for familial hypercholesterolemia. Her last menstrual period was 12 days ago. At the initial visit, blood pressure was 158/94 mm Hg; serum creatinine level was 2.1 mg/dL (estimated glomerular filtration rate, 35 mL/min/1.73 m^2); urine microscopy showed 41-50 red blood cells and occasional red blood cell casts; and urine protein/creatinine ratio was 2,973 mg/g. Other laboratory findings included increased levels of antinuclear antibody and anti–double-stranded DNA antibody. Complement C3 and C4 levels were low. Lisinopril 10 mg daily was started, and kidney biopsy was performed. Results were consistent with class IV lupus nephritis. Prednisone and mycophenolate mofetil were initiated. Which of the following is a potential complication of this immunosuppressive regimen?

a. Hypercalcemia
b. Increased risk of rhabdomyolysis
c. Teratogenicity
d. Hypersomnolence

VIII.16. A 52-year-old woman is evaluated for 2 episodes of painless gross hematuria over the past week. She also has noted intermittent abdominal pain and a rash on her legs. The rash did not improve with application of topical over-the-counter hydrocortisone cream. She has had several episodes of loose bowel movements and reports no nausea and vomiting. Her medical history includes hypothyroidism and hyperlipidemia. Her last menstrual period was approximately 8 months ago. Medications are levothyroxine and simvastatin. Vital signs are blood pressure 154/88 mm Hg, pulse 84 beats/min, respiratory rate 16 breaths/min, temperature 37.6°C, and weight 88 kg. Physical examination discloses mild diffuse abdominal tenderness without rigidity, distension, guarding, or rebound and a purpuric rash over the buttocks and legs. Other examination findings are within normal limits.

Laboratory studies show serum creatinine 0.9 mg/dL (estimated glomerular filtration rate, >60 mL/min/1.73 m^2). Results of complete blood count, international normalized ratio, activated partial thromboplastin time, electrolyte panel, glucose, aspartate aminotransferase, complement levels C3 and C4, serum immunofixation, serum immunoglobulin light chains, antinuclear antibody, and antibodies to hepatitis B and C, HIV, double-stranded DNA, proteinase 3, and myeloperoxidase are all within normal limits. Urinalysis shows 1+ protein and 3+ hemoglobin. Urine microscopy shows 11-20 red blood cells and 1-3 white blood cells per high-power field. Urine Gram stain is negative; 24-hour urine total protein level is 360 mg. Computed tomography urography findings are within normal limits. Biopsy of a skin lesion shows leukocytoclastic vasculitis with positive immunoglobulin (Ig) A staining of vessels on immunofluorescence. In addition to close monitoring of serum creatinine value, urinalysis, and urinary protein levels, which of the following regimens should be initiated?

a. Lisinopril 20 mg daily
b. Lisinopril 20 mg daily and prednisone 80 mg daily
c. Lisinopril 20 mg daily and 1 g intravenous methylprednisolone for 3 days, followed by prednisone 80 mg daily
d. Lisinopril 20 mg daily and 1 g intravenous methylprednisolone for 3 days, followed by prednisone 80 mg daily and oral cyclophosphamide 150 mg daily

Answers

VIII.1. Answer d.

To analyze the patient's acid-base status:

Step 1: Her pH of 7.32 indicates acidemia.

Step 2: Her serum [HCO_3^-] is decreased, in the same direction as the blood pH. This establishes that the primary alteration is metabolic.

Step 3: The Pco_2 is decreased, which could represent respiratory compensation. Using the Rule of 15, the expected Pco_2 should be 32 mm Hg (17+15), which indicates metabolic acidosis with appropriate compensation.

Step 4: Calculating the anion gap gives 12 mmol/L (135–106–17), which indicates normal anion gap acidosis.

Given her mild to moderate kidney dysfunction and background of diabetes mellitus, the most likely diagnosis is the type 4 hyporeninemic hypoaldosteronism type of renal tubular acidosis. Distal and proximal renal tubular acidosis are incorrect because they are typically associated with hypokalemia, not hyperkalemia. Therefore, on the basis of the clinical scenario and laboratory results, respiratory acidosis is incorrect.

VIII.2. Answer b.

To analyze the patient's acid-base status:

Step 1: His pH is 7.32; he has acidemia.

Step 2: His [HCO_3^-] is 25 mmol/L, which is not consistent with acidosis. His PCO_2 is increased to 49 mm Hg, which is in the direction of acidosis. The primary event in his acid-base status is respiratory acidosis.

Step 3: He has acute flail chest, his breathing is shallow, and he received narcotics that prevented tachypnea. His serum [HCO_3^-] increased by about 1 mmol/L, which fits well with acute respiratory acidosis. For each 10-mm Hg increase in Pco_2, the serum [HCO_3^-] increases by ≈0.8-1.0 mmol/L.

He has acute respiratory acidosis with appropriate metabolic compensation. Therefore, on the basis of the clinical scenario and laboratory results, the other choices are incorrect.

VIII.3. Answer b.

To analyze the patient's acid-base status,

Step 1: Her pH is 7.30; she has acidemia.

Step 2: Her serum [HCO_3^-] is decreased, consistent with metabolic acidosis.

Step 3: Checking the compensation with the Rule of 15 shows that her expected Pco_2 is 29 mm Hg. Thus, she has a metabolic acidosis with appropriate respiratory compensation.

Step 4: Calculating the anion gap gives 22 mmol/L (136–100–14).

This patient is malnourished and has a prior history of alcohol abuse. She has a high anion gap acidosis with appropriate respiratory compensation. She most likely has limited glutathione reserve, which could be easily depleted due to regular acetaminophen use. Measurement of oxoproline levels would be most relevant. Oxoproline is an acid that can increase in chronic acetaminophen use. Her clinical history does not fit D-lactate accumulation. She has not been receiving any intravenous infusion that might contain propylene. Moreover, her lactate level was normal. Her history does not support active drug intoxication.

VIII.4. Answer c.

The most likely diagnosis in this patient is an acute respiratory acidosis. This is based on his acute acidemia and increased Pco_2. Clinical features that support this diagnosis include his COPD, obesity, narcotic use, and low respiration rate. The expected bicarbonate compensation is calculated by dividing the change in Pco_2 by 10. Thus, the expected [HCO_3^-] is an increase of 4 mmol/L, which is in line with his laboratory values. This means that no secondary acid-base disorder is present. To confirm this, his calculated anion gap is 10 mmol/L, which is within the normal range. On the basis of these findings and calculations, the other answers, including normal anion gap metabolic acidosis, chronic respiratory acidosis, and mixed acute and chronic respiratory acidosis are not present in this patient.

VIII.5. Answer a.

This patient has acute kidney injury in the setting of rhabdomyolysis after a seizure. Myoglobin released during muscle breakdown is nephrotoxic, which results in pigment-induced nephropathy that causes acute tubular injury. Increased aspartate aminotransferase and markedly increased serum creatine kinase levels are seen in this disorder. Urinalysis typically shows the presence of blood (because the test also detects pigments such as myoglobin and hemoglobin) and protein, whereas red blood cells are absent on urine microscopic examination. The most appropriate initial therapy is administration of 0.9 N saline IV to achieve a urine output of 200 to 300 mL/h. Although urinary alkalization has been recommended in the past, there are no randomized trials to support this, and administering a bolus of sodium bicarbonate is not indicated in the setting of mildly decreased serum bicarbonate level. Administration of furosemide initially in a patient who is not volume overloaded is incorrect. IV calcium replacement is inappropriate to treat mild hypocalcemia or mild hyperkalemia.

VIII.6. Answer b.

The most likely diagnosis is renal atheroemboli. Atheroembolic events can occur within several days to several weeks after coronary arteriography as a result of disruption of atheromatous plaques in the aorta during the procedure. Livedo reticularis is a cutaneous manifestation of atheroembolic disease. Although urine findings are not sensitive or specific, leukocyturia and eosinophiluria may be present. Cardiorenal syndrome occurs when dysfunction of either the heart or kidneys induces dysfunction of the other, and this patient does not have clinical evidence of heart failure. Initiation of angiotensin-converting enzyme inhibitors (such as lisinopril) and angiotensin II receptor blockers typically causes a reversible decrease in glomerular filtration rate because they block the effect of angiotensin on renal efferent arteriolar tone. This patient has been on lisinopril chronically with no change in dose during the period in which AKI developed. Thus, the decrease in kidney function would not be related to an effect of lisinopril. Contrast-associated AKI can occur after arterial administration of iodinated contrast, typically peaks within 2 to 5 days, and is not associated with livedo reticularis.

VIII.7. Answer d.

This patient has HRS, defined as 1) no improvement in SCr after 2 days of diuretic withdrawal and volume expansion with albumin (1 g/kg per day), 2) no other apparent reason for acute kidney injury, such as recent administration of nephrotoxic drugs or shock, 3) no signs of structural kidney injury, with proteinuria <500 mg/d and <50 RBCs per high-power field, and 4) normal findings on renal ultrasonography. HRS can be precipitated by worsening liver function, bleeding, infection (such as spontaneous bacterial peritonitis), and large-volume paracentesis without albumin replacement. Patients with hepatitis C can also have development of glomerular diseases, commonly cryoglobulinemia and immune complex–mediated glomerulonephritis. With these conditions, greater degrees of microhematuria are present, and urinary protein levels are higher. Acute interstitial nephritis (AIN) due to medications is another possibility in this patient, given the recent addition of furosemide, which has a sulfa moiety and can cause interstitial nephritis. However, patients with AIN typically have pyuria and nonnephrotic proteinuria, although the classic triad of fever, rash, and eosinophiluria is relatively uncommon. The overall clinical context is more consistent with HRS.

VIII.8. Answer b.

This patient should continue his current therapy given the potential benefit of therapy (ie, cardiovascular risk factors) and minimal risks. Current guidelines do not suggest routine monitoring of LDL levels in patients on dialysis, and currently there is no target cholesterol level in this group. Among patients at all stages of chronic kidney disease, those on dialysis derive the least benefit from statin therapy; thus, patients on dialysis should not be started on a statin, but statin therapy should not be discontinued if the patient is tolerating it well.

VIII.9. Answer a.

Proton pump inhibitors are the only medications in this list not associated with hyperkalemia.

VIII.10. Answer b.

Anemia of chronic disease is usually a normocytic anemia associated with low transferrin level and low transferrin saturation. Iron deficiency anemia is associated with microcytosis, high transferrin level, low transferrin saturation, and low ferritin. Macrocytosis is not a common feature of CKD but is often associated with vitamin B_{12} or folate deficiency. Option d is incorrect because the anemia of CKD is associated with low transferrin saturation rather than high transferrin saturation. Ferritin levels are not reliable in patients with CKD because ferritin is an acute phase protein.

VIII.11. Answer b.

This patient has new-onset respiratory symptoms, and computed tomography showed a mass lesion. The most likely diagnosis is SIADH due to ectopic production of arginine vasopressin from small cell lung carcinoma. His volume status is adequate. He had a history of alcohol use, but there is no sign of liver disease. Hyponatremia in cirrhosis and liver failure typically develops in the setting of total body volume expansion with evidence of ascites and edema and reduced systolic blood pressure. Patients with beer potomania as the cause of hyponatremia typically show maximally diluted urine. Given the patient's preserved kidney function, the urine should be maximally diluted to an osmolality of <100 mOsm/kg.

VIII.12. Answer c.

Common causes of hypokalemia include large-volume diarrhea, medications such as diuretics, renal tubular acidosis, and transcellular shifts. In this case, there was no reported diarrhea, evidence of acidosis, or noninsulin medications that would cause hypokalemia. The rapid onset of her hypokalemia suggests the possibility of a transcellular shift. Her history of depression, availability of insulin, hypoglycemia, and examination findings of diaphoresis and somnolence suggest insulin intoxication. Insulin will shift potassium intracellularly causing hypokalemia. Renal tubular acidosis and hyperaldosteronism would not be causes of acute hypokalemia. Periodic paralysis can be associated with hypokalemia, but there should be a history of paralysis, which was not evident in this case.

VIII.13. Answer a.

In this case, her urine osmolality was inappropriately low (<200 mOsm/kg). An appropriate response in her urine osmolality would have been greater than 600 mOsm/kg. This suggests diabetes insipidus as the cause of her hypernatremia. To distinguish between central and nephrogenic diabetes insipidus, desmopressin is given with the help of a nephrologist. Because this information is not given in the question, the clinical context is important. In this case, the most likely cause of her hypernatremia is drug-induced nephrogenic diabetes insipidus secondary to lithium. Osmotic diuresis, accidental diuretic administration, and insufficient water intake would be less likely on the basis of the laboratory findings and clinical presentation.

VIII.14. Answer a.

This patient has pre-existing stage 3a chronic kidney disease with microalbuminuria, which is consistent with diabetic nephropathy (DN), and worsening kidney function, sterile pyuria, and nonnephrotic-range proteinuria out of proportion to the degree of microalbuminuria have developed. The proteinuria is not due to a urinary monoclonal protein, which also would show an increased total urinary protein level out of proportion to microalbuminuria. These findings suggest inflammation and tubular proteinuria, and, along with the significant decrease in kidney function, are not expected in progressive DN. With tubulointerstitial disease, tubular proteinuria occurs, which includes proteins such as α1-microglobulin and retinol binding protein. A kidney biopsy is the only way to confirm a diagnosis of interstitial nephritis, which in this patient could be due to pantoprazole because proton pump inhibitors are known to cause this condition. Although worsening kidney function in patients with diabetes mellitus is often attributed to progressive DN, other kidney disorders also can develop in patients with DN which would alter management; thus, a kidney biopsy is indicated if the presentation is atypical for DN. In fact, less than half of kidney biopsies performed in patients with diabetes mellitus show DN alone. This patient does not have hydronephrosis or hematuria to suggest obstructive uropathy due to urolithiasis, and thus CT of the abdomen and pelvis without contrast is not indicated. Rather than immediate discontinuation of lisinopril, the diagnosis must be made with kidney biopsy. Renovascular disease can result in decreased kidney function, but worsening hypertension would also be expected. Renovascular disease also does not present with urinary markers of tubulointerstitial disease; thus, performing Doppler ultrasonography of the renal arteries is incorrect.

VIII.15. Answer c.

Mycophenolate mofetil is a pregnancy category D medication because of the increased risk of first-trimester pregnancy loss and congenital malformations. All women of reproductive potential for whom mycophenolate mofetil is prescribed must be informed of these risks and agree in writing to use birth control while taking it and for 6 weeks after stopping treatment, as part of the Mycophenolate Risk Evaluation and Mitigation Strategy. Mycophenolate mofetil would not be expected to cause hypercalcemia, although prednisone may uncommonly be associated with hypocalcemia. The risk of rhabdomyolysis is increased in patients taking a statin along with other immunosuppressive medications, such as cyclosporine or tacrolimus, but not mycophenolate mofetil. Patients taking prednisone may have development of a steroid-induced myopathy rather than rhabdomyolysis. Both prednisone and mycophenolate mofetil have been associated with insomnia, and hypersomnolence would be unexpected.

VIII.16. Answer a.

This patient has Henoch-Schönlein purpura, a systemic IgA vasculitis affecting the skin, kidneys, gastrointestinal tract, and joints. In adults, the renal presentation and prognosis vary. In patients such as this with normal kidney function and proteinuria <500 mg/d, treatment is generally supportive, including use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker to decrease proteinuria and control blood pressure. Kidney function and proteinuria must be monitored closely and a kidney biopsy performed if these worsen. Additional immunosuppressive therapy including corticosteroids is used in patients with impaired kidney function, proteinuria >500 to 1,000 mg/d, and/or glomerular crescents on kidney biopsy. The addition of cytotoxic medication such as cyclophosphamide may be considered in patients with more severe or progressive disease.

Section

IX

Neurology

56

Cerebrovascular Diseases

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Ischemic Cerebrovascular Disease

Pathophysiologic Mechanisms

The causes of ischemic cerebrovascular disorders, including transient ischemic attack (TIA) and cerebral infarction, can be classified according to the site of the source for the arterial blockage within the vascular system, from most proximal to distal (Figure 56.1):

1. *Cardiac source*: arrhythmias (eg, atrial fibrillation) and structural disease (eg, valve disease, dilated cardiomyopathy, or recent myocardial infarction); paradoxical emboli with a right-to-left shunt through a patent foramen ovale, although most patients with patent foramen ovale are asymptomatic
2. *Large-vessel disorders*: most commonly atherosclerosis or dissection in the carotid or vertebrobasilar system; the aorta is uncommonly a source of embolus
3. *Small-vessel occlusive disease*: inflammatory or noninflammatory arteriopathies (eg, hypertension-induced disease is most common; isolated central nervous system angiitis, systemic lupus erythematosus, and others are rare)
4. *Hematologic disorders*: disorders of hemoglobin, white blood cells, and platelets (polycythemia, sickle cell anemia, and severe leukocytosis caused by blast crisis in acute leukemia thrombocytosis); hypercoagulable states (including antithrombin III deficiency), protein C deficiency, protein S deficiency, hereditary resistance to activated protein C, anticardiolipin antibody syndrome, lupus anticoagulant positivity, and hypercoagulable states caused by carcinoma (factor V Leiden mutation is a risk factor for venous thrombosis but in general not for arterial thrombosis).

Notably, illicit drug use is a common cause of stroke in young persons; it may cause arrhythmia, inflammatory arteriopathies, and a relative hypercoagulable state.

Transient Ischemic Attacks

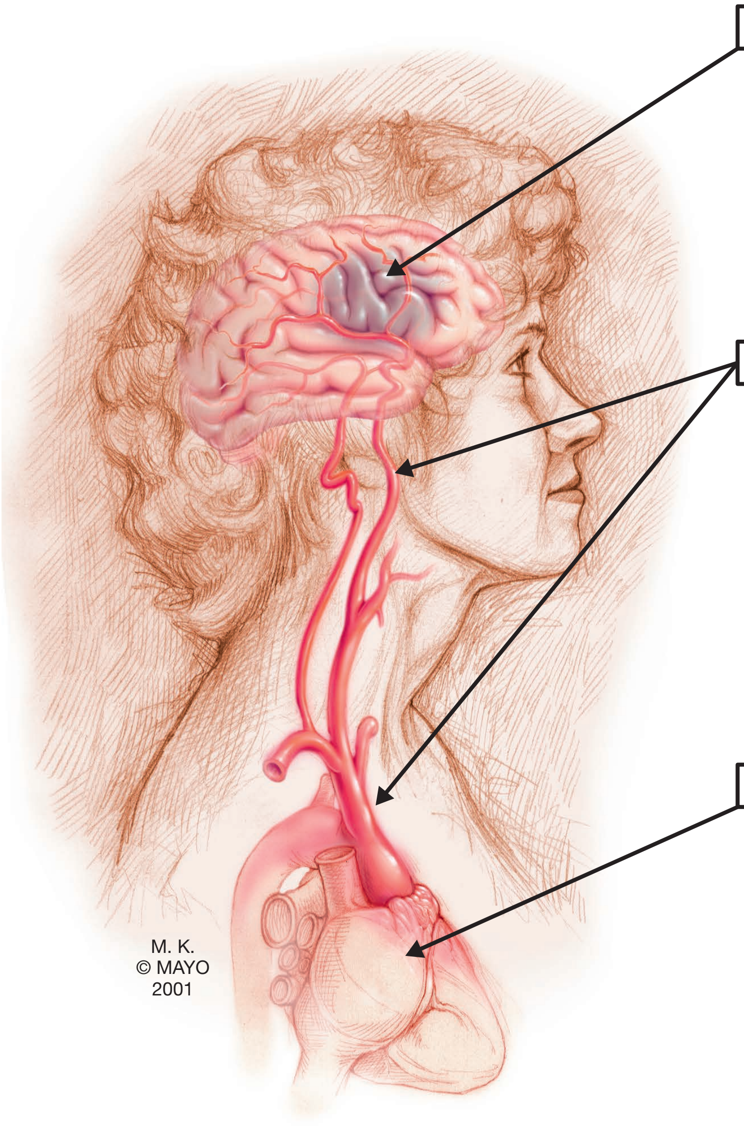
A **TIA** is any transient neurologic dysfunction caused by cerebral ischemia that does not result in cerebral infarction. Patients who experience a TIA are at high risk for subsequent cerebral infarctions: 4% to 10% within 1 year and up to 33% within a patient's lifetime. The duration of most TIAs is less than 15 minutes; about 90% resolve within 1 hour. Patients with cerebral infarcts, hemorrhages, and mass lesions and metabolic disorders such as hypoglycemina can present with transient symptoms like those of TIAs.

Key Definition

Transient ischemic attack: *any transient neurologic dysfunction as a result of cerebral ischemia that does not result in cerebral infarction.*

The long-term prognosis for patients who have a TIA generally follows the *rule of 3s*: one-third will have cerebral infarction, one-third will have at least 1 more TIA, and one-third will have no more TIAs. The following features increase the risk of stroke after TIA: age older than 60 years, hypertension, weakness or speech disturbance with TIA, TIA duration of more than 60 minutes, and diabetes mellitus.

TIAs, like stroke, can cause various neurologic symptoms, but classically they produce speech, language, motor, or sensory dysfunction. A classic example is **amaurosis fugax**, which



Small artery ~35%

- Noninflammatory
  - Atherosclerosis
  - Lipohyalinosis
- Inflammatory
  - Vasculitis (eg, primary central nervous system vasculitis)

Large artery ~25%

Intracranial: cerebral arteries

Extracranial: aorta, vertebral and carotid arteries

- Noninflammatory
  - Atherosclerosis
  - Dissection
- Inflammatory
  - Vasculitis (eg, giant cell arteritis)

Cardioembolic ~35%

- Arrhythmias
  - Atrial fibrillation
- Structural
  - Valvular disease
  - Recent myocardial infarction
  - Patent foramen ovale with paradoxical embolus

Coagulopathies ~5%

- Disorders of main blood products
  - Sickle cell disease, acute leukemia, thrombocytosis
- Other hematologic disorders leading to procoagulant state

Figure 56.1. Causes of Ischemic Cerebrovascular Disease. Sites of source for arterial blockage within the vascular system are listed with corresponding frequencies.

is defined as temporary, partial, or complete monocular blindness and is a symptom of carotid artery disease. Glaucoma, vitreous hemorrhage, retinal detachment, papilledema, migrainous aura, temporal arteritis, and even ectopic floaters can mimic amaurosis fugax.

Key Definition

Amaurosis fugax: *temporary, partial, or complete monocular blindness (a symptom of carotid artery disease).*

Management of Acute Cerebral Infarction

If a patient has a severe neurologic deficit caused by an acute cerebral infarction, the immediate decision in the emergency department is whether the patient is a candidate for an intervention: either thrombolytic therapy (tissue plasminogen activator [tPA]) or endovascular therapy. The initial therapeutic approach to ischemic infarction depends greatly on the time from the onset of symptoms to the presentation for emergency medical care. If the onset of symptoms was less than 3 hours before the evaluation, emergency thrombolytic therapy should be considered. If a patient awakens from sleep with the deficit, thrombolytic therapy should not be considered unless the duration of the deficit is clearly less than 3 hours. Data do suggest that select patients may benefit from the use of tPA up to 4.5 hours after symptom onset, and most institutions use 4.5 hours as the cutoff for the use of tPA. The treatment window for endovascular therapy is somewhat longer and is a topic of ongoing research.

Computed tomographic (CT) findings are important in selecting patients for tPA. Noncontrast CT should not show any evidence of intracranial hemorrhage, mass effect, early evidence of a large cerebral infarction (greater than one-third of the cerebral hemisphere distribution), or midline shift. Patients with the following clinical criteria may be excluded: rapidly improving deficit, obtunded or comatose status or presentation with seizure, history of intracranial hemorrhage or bleeding diathesis, blood pressure elevation persistently greater than 185/110 mm Hg, gastrointestinal tract hemorrhage or urinary tract hemorrhage within the previous 21 days, traumatic brain injury or cerebral infarction within 3 months, or mild deficit. Eligible patients should have marked weakness in at least 1 limb or severe aphasia. Laboratory abnormalities that may preclude treatment are heparin use within the previous 48 hours with an increased activated partial thromboplastin time, international normalized ratio (INR) greater than 1.7, or blood glucose concentration less than 50 mg/dL.

Intravenous (IV) tPA improves neurologic status at 3 months after stroke compared with placebo. In 1 clinical trial, a greater proportion (about 12% larger) of patients who received tPA within 3 hours had minimal or no deficit at 3 months after the event, and the proportion of persons who died was not increased. This finding is particularly important because the tPA group had an increased occurrence of symptomatic hemorrhage (6.4% compared with 0.6%).

Endovascular therapy, which involves mechanical removal of a clot with an intra-arterial, catheter-based retrieval device, is a newer treatment option for patients with ischemic stroke resulting from a proximal large-artery occlusion. For those patients, endovascular therapy is superior to standard treatment with IV tPA alone and results in a 46% rate of functional independence compared with 27% for tPA alone. Some patients who are eligible for endovascular therapy may not be candidates for IV tPA. However, if patients are eligible for tPA, they should be treated with IV tPA before endovascular therapy is considered.

To be eligible for endovascular treatment, patients must have a proximal large-artery occlusion that can be retrieved, so vessel imaging, usually with CT angiography, is a necessary part of the acute evaluation. Like tPA, endovascular therapy has a limited window. Current guidelines recommend that endovascular therapy be initiated within 6 hours after stroke onset. However, recent clinical trial data suggest that the window can be extended up to 24 hours with the use of a tissue-based approach instead of a strictly time-based approach. Advanced perfusion imaging studies with CT or magnetic resonance imaging techniques can be used to assess whether brain tissue is salvageable and therefore whether a patient would benefit from endovascular therapy. Eligibility and patient selection for endovascular therapy is an area of active research.

Risk Factors

Risk factors for atherosclerotic occlusive disease are similar to those for coronary artery disease: hypertension, cigarette smoking, diabetes mellitus, hypercholesterolemia, male sex, and advanced age. Emboli from intracardiac mural thrombi also cause TIA and cerebral infarction. Proven cardiac risk factors include atrial fibrillation (including paroxysmal and persistent atrial fibrillation), atrial flutter, dilated cardiomyopathy, mechanical valve, rheumatic valve disease, and recent myocardial infarction (Box 56.1).

Hypertension is the most important modifiable risk factor for stroke, but other modifiable risk factors include cigarette smoking, diabetes mellitus, hypercholesterolemia, metabolic syndrome, sedentary lifestyle, obesity, obstructive sleep apnea, and, possibly, increased homocysteine level. Although low levels of alcohol consumption seem to have a protective effect for ischemic stroke, heavy alcohol consumption increases a person's risk for all types of stroke, particularly intracerebral and subarachnoid hemorrhage.

Stroke Risks With Nonvalvular Atrial Fibrillation

Atrial fibrillation is associated with up to 24% of ischemic strokes. The stroke rate for the entire cohort of patients with chronic atrial fibrillation is generally about 5% per year. However, patients younger than 60 years with lone atrial fibrillation have a lower risk for stroke than other patients with atrial fibrillation and often receive treatment with only aspirin, depending on their CHADS_2 score (which includes points for congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and previous stroke, TIA, or systemic thromboembolism) or CHA_2DS_2-VASc score (which includes

Box 56.1 • Cardiac Risk Factors for Cerebral Infarction or Transient Ischemic Attack

Proven cardiac risk factors

- Atrial fibrillation
- Paroxysmal atrial fibrillation
- Atrial flutter
- Dilated cardiomyopathy
- Mechanical valve
- Rheumatic valve disease
- Recent (within 1 mo) myocardial infarction
- Intracardiac thrombus
- Intracardiac mass (ie, atrial myxoma or papillary fibroelastoma)
- Infectious endocarditis
- Nonbacterial thrombotic endocarditis

Putative or uncertain cardiac risk factors

- Sick sinus syndrome
- Patent foramen ovale with or without atrial septal aneurysm
- Atherosclerotic debris in the thoracic aorta
- Spontaneous echocardiographic contrast
- Myocardial infarction 2-6 mo earlier
- Hypokinetic or akinetic left ventricular segment
- Calcification of mitral annulus

points for congestive heart failure, hypertension, age, diabetes mellitus, history of stroke or TIA or systemic thromboembolism, vascular disease, and female sex) (See Table 3.4). Patients with atrial fibrillation whose predictive scores suggest an intermediate or high risk for a thromboembolic event generally should receive anticoagulation with warfarin (INR, 2.0-3.0) or a direct oral anticoagulant, such as the direct factor Xa inhibitors (apixaban, rivaroxaban, or edoxaban) or the direct thrombin inhibitors (dabigatran). Patients at low risk should receive aspirin.

For patients receiving anticoagulant therapy with warfarin, the dominant risk factor for intracranial hemorrhage is the INR, but age is another risk factor for subdural hemorrhage. An INR of 2.0 to 3.0 is probably an adequate level of anticoagulation for nearly all warfarin indications except for preventing embolization from mechanical heart valves. Generally, the lowest effective intensity of anticoagulant therapy should be given.

Percutaneous atrial appendage closure may be considered for selected patients with an unacceptable risk for anticoagulation but with a moderate or high risk for atrial fibrillation–related stroke according to their $CHADS_2$ or CHA_2DS_2-VASc score.

KEY FACTS

✓ Risk for subsequent cerebral infarctions is high after a TIA, ranging from 4%-10% within 1 year to 33% within a patient's lifetime

✓ Management of acute cerebral infarction—

- emergency thrombolytic therapy should be considered if symptom onset was <3 hours before evaluation
- if patient awakens from sleep with the deficit, thrombolytic therapy should not be considered unless the duration of the deficit is clearly <3 hours
- for selecting use of tPA, noncontrast CT should not show any evidence of intracranial hemorrhage, mass effect, early evidence of a large cerebral infarction (larger than one-third of the distribution of the cerebral hemisphere), or midline shift

✓ Modifiable risk factors for stroke: hypertension is the most important; others include cigarette smoking, diabetes mellitus, hypercholesterolemia, metabolic syndrome, sedentary lifestyle, obesity, and obstructive sleep apnea

✓ Treatment of patients with atrial fibrillation—those whose predictive scores suggest an intermediate or high risk for a thromboembolic event generally should receive anticoagulation with warfarin (INR, 2.0-3.0); those at low risk should receive aspirin

Secondary Stroke Prevention

Carotid Endarterectomy and Carotid Angioplasty With Stent Placement

Carotid endarterectomy markedly decreases the risk of stroke and death of *symptomatic* patients who have a 70% to 99% stenosis of the carotid artery. For a 50% to 69% stenosis, carotid endarterectomy is moderately efficacious in select symptomatic patients. Medical treatment alone is better than carotid endarterectomy for patients with a stenosis of 49% or less. Symptoms must be those of a carotid territory TIA or minor stroke and must be of recent onset (<4 months). To have a favorable risk-benefit ratio, the perioperative complication rate must be low.

Carotid angioplasty with stent placement may be used as an alternative to carotid endarterectomy, particularly for high-risk patients, such as those who previously had carotid endarterectomy, radiotherapy to the neck, or neck dissection; those with a stenosis high in the internal carotid artery; or those otherwise deemed at high risk for the operation. The overall short-term and long-term risks (stroke, myocardial infarction, and death combined) of endarterectomy and endovascular treatment are similar. The periprocedural risk of ischemic stroke is somewhat higher with endovascular treatment, and the risk of myocardial infarction is somewhat higher with endarterectomy.

Select patients with an *asymptomatic* carotid stenosis of at least 60% may also benefit from carotid endarterectomy (ie, they have a decreased risk of future ipsilateral stroke or related death). In clinical trials that compared the use of aspirin and risk-factor reduction with carotid endarterectomy, the risk of stroke was low for patients treated surgically and for those treated medically. In the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial, the 5-year risk of ipsilateral stroke or death was about 2% per year for patients treated medically and 1% per year for those treated surgically. As with symptomatic patients, for treatment to be of benefit to asymptomatic patients, the perioperative complication rate must be low (surgeons and hospitals in the ACAS had perioperative complication rates <3%), and carotid angioplasty with stent placement may be used as an alternative to carotid endarterectomy in select asymptomatic patients.

Patients with asymptomatic carotid occlusive disease who require an operation for another reason (eg, coronary artery bypass grafting or abdominal aortic aneurysm repair) usually can have that procedure performed without prophylactic carotid endarterectomy, because in this context the risk of stroke in asymptomatic persons is quite low. For patients with symptoms in the distribution of a stenotic carotid artery, the decision is more complicated. Generally, if a patient with an asymptomatic carotid stenosis has cardiac symptoms (eg, angina), coronary artery bypass grafting or angioplasty is performed first; if the patient is otherwise a good candidate for a carotid procedure, carotid endarterectomy or carotid angioplasty with stent placement is then performed.

Antiplatelet Agents

Aspirin, aspirin in combination with extended-release dipyridamole, and clopidogrel are all effective for secondary prevention of noncardioembolic ischemic stroke or TIA. Although the optimal dose of aspirin is uncertain (trials have examined doses from 20-1,300 mg daily), most studies have shown that 50 to 325 mg daily is as efficacious as higher doses. The guideline from the American College of Chest Physicians recommends aspirin at a dose of 75 to 100 mg daily. Clopidogrel is given as a single dose of 75 mg daily. Low-dose aspirin in combination with extended-release dipyridamole provides another useful alternative to aspirin alone for prevention of stroke. The combination may be slightly more effective than aspirin alone for secondary stroke prevention.

Ticlopidine is also an effective antiplatelet agent, but it is rarely used because of associated neutropenia (thus, a complete blood cell count must be monitored every 2 weeks for the first 3 months of treatment) and thrombotic thrombocytopenic purpura, which has rarely been reported with clopidogrel. Another antiplatelet agent, ticagrelor, is being investigated for secondary stroke prevention, but current evidence suggests that it is not superior to aspirin.

The use of clopidogrel in combination with aspirin (dual antiplatelet therapy) may be beneficial in select circumstances, such as short-term therapy (90 days) for patients with symptomatic intracranial stenosis. Shorter-term use (21 days) of dual antiplatelet therapy with clopidogrel and aspirin also appears to be beneficial in prevention of ischemic stroke in those with noncardioembolic ischemic stroke or TIA. The use of aspirin with clopidogrel for longer periods does not provide additional benefit, but it does increase the risk of bleeding; therefore, the combination is not commonly used for long-term stroke prevention.

Anticoagulants

Warfarin is used for secondary prevention in select patients who have TIA or cerebral infarction and 1) specific cardiac sources of emboli (eg, atrial fibrillation, left atrial or ventricular clot, mechanical heart valves, recent myocardial infarction with left ventricular thrombus, or valvular thrombus) or 2) hypercoagulable states. Warfarin may also be recommended for patients with TIA or cerebral infarction and aortic arch thrombus and for those with extracranial dissection; no clinical trial data support this treatment approach, though, and aspirin is sometimes recommended instead of warfarin for these conditions. In a clinical trial with patients who had symptomatic intracranial stenosis, warfarin was not more effective than aspirin for reducing ischemic stroke risk and was associated with a higher risk of hemorrhage.

Direct oral anticoagulants, including direct factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban) and direct thrombin inhibitors (dabigatran), are approved for secondary stroke prevention for patients with nonvalvular atrial fibrillation, but they have not been approved for patients with hypercoagulable disorders, although this is an area of active research. The direct oral anticoagulants should not be used in patients with a mechanical heart valve.

KEY FACTS

- ✓ Carotid endarterectomy—markedly decreases the risk of stroke and death of *symptomatic* patients who have a 70%-99% stenosis of the carotid artery
- ✓ Aspirin, aspirin in combination with extended-release dipyridamole, and clopidogrel—all are effective for secondary prevention of noncardioembolic ischemic stroke or TIA
- ✓ Use of aspirin in combination with clopidogrel for long periods (>90 days)—no additional benefit, but it does increase the risk of significant bleeding; thus, the combination is not commonly used as long-term stroke prevention
- ✓ Warfarin—used for secondary prevention in select patients who have TIA or cerebral infarction and 1) specific cardiac sources of embolus or 2) hypercoagulable states

Hemorrhagic Cerebrovascular Disease

Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) is the second most common cause of stroke, accounting for 10% to 30% of all nonischemic strokes. Hypertension and cerebral amyloid angiopathy account for most primary hemorrhages, but ICH can also be caused by trauma and structural lesions (eg, primary and metastatic tumors, arteriovenous malformation, and cavernous malformation). Hypertension commonly affects deep penetrating cerebral vessels, especially those supplying the basal ganglia, cerebral white matter, thalamus, pons, and cerebellum. Therefore, most hemorrhages due to hypertension occur in these regions of the brain. In contrast, cerebral amyloid angiopathy usually causes lobar hemorrhages.

The symptoms of ICH can be identical to those of an ischemic stroke, and patients with ICH often (but not always) complain of a headache. Imaging is therefore necessary to differentiate between ischemia and hemorrhage.

Surgical evacuation of an ICH may be necessary for patients who have signs of increased intracranial pressure or for those whose condition is worsening. However, apart from data for select patients with lobar hemorrhages, no data clearly show that surgery is beneficial for ICH.

Prognosis depends on the size and location of the hemorrhage. Factors that increase mortality are patient age older than 80 years, hemorrhage volume of more than 30 mL, an initial Glasgow Coma Scale score less than 13, extension of the hemorrhage into the ventricular system, and an infratentorial hemorrhage location.

Cerebellar Hemorrhage

Cerebellar hemorrhage must be recognized because surgical drainage may be lifesaving. The important clinical findings are vomiting and inability to walk (ataxia). Long-tract signs, such as hemiparesis, are usually absent. Cerebellar hemorrhage can cause obstructive hydrocephalus, and patients may have ipsilateral gaze palsy (cranial nerve VI palsy) or ipsilateral facial weakness (cranial nerve VII palsy). They may or may not have headache, vertigo, or lethargy.

Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) accounts for about 5% of strokes, including about half of those in patients younger than 45 years; the peak age ranges from 35 to 65 years. The most common cause of nontraumatic SAH is intracranial saccular aneurysm. In up to 50% of cases of SAH, a patient with an aneurysm may have a small sentinel bleed with a warning headache, or the expansion of an aneurysm may cause focal neurologic signs

Box 56.2 • Differential Diagnosis of Subtypes of Hemorrhagic Cerebrovascular Disease

- Hemorrhage into parenchyma
  - Hypertension
  - Amyloid angiopathy
  - Aneurysm
  - Vascular malformation
    - Arteriovenous malformation
    - Cavernous malformation
    - Dural arteriovenous fistula
  - Trauma—primarily frontal and temporal
  - Hemorrhagic infarction
  - Secondary to brain tumors (primary and secondary neoplasms)
  - Inflammatory diseases of the vasculature
  - Disorders of blood-forming organs (blood dyscrasia, especially leukemia and thrombocytopenic purpura)
  - Anticoagulant or thrombolytic therapy
  - Increased intracranial pressure (brainstem) (Duret hemorrhages)
  - Illicit drug use (cocaine or amphetamines)
  - Postsurgical bleeding
  - Fat embolism (petechial)
  - Hemorrhagic encephalitis (petechial)
  - Undetermined cause (normal blood pressure and no other recognizable disorder)
- Hemorrhage into subarachnoid space (subarachnoid hemorrhage)
  - Trauma
  - Aneurysm
    - Saccular (berry, congenital)
    - Fusiform (arteriosclerotic)—rarely causes hemorrhage
    - Mycotic
  - Arteriovenous malformation
  - Many of the same causes listed under "Hemorrhage into parenchyma" above
- Subdural and epidural hemorrhage (hematoma)
  - Mainly traumatic (especially during anticoagulation)
  - Many of the same causes listed under "Hemorrhage into parenchyma" above
- Hemorrhage into the pituitary (pituitary apoplexy)

or symptoms (eg, an incomplete cranial nerve III palsy). The prognosis is related directly to the state of consciousness at the time of intervention. Onset of the headache is characteristically sudden (thunderclap), and although one-third of SAHs occur during exertion, one-third occur during rest or minimal activity, and one-third occur during sleep. Complications of SAH include intracranial arterial vasospasm, with an incidence that peaks in 4 to 12 days after the initial hemorrhage. Other potential SAH complications include hyponatremia associated with a cerebral salt-wasting syndrome or the syndrome of inappropriate secretion of antidiuretic hormone, communicating hydrocephalus, seizures, and aneurysm rebleeding. In addition to the initial hemorrhage, vasospasm and subsequent hemorrhage are the leading causes of morbidity and death among patients who have SAH. The outpouring of catecholamines may cause myocardial damage and accompanying electrocardiographic abnormalities, pulmonary edema, and arrhythmias. Arrhythmias can be both supraventricular and ventricular and are most likely to occur during the initial hours or days after a moderate to severe SAH.

Initial treatment is supportive, often in an intensive care unit. Vasospasm is best prevented with the maintenance of normal or increased blood pressure and intravascular volume and with use of the calcium channel blocker nimodipine. If the SAH is from a ruptured aneurysm, an experienced team often does early intervention (surgical clipping or endovascular coiling).

The differential diagnosis of subtypes of hemorrhagic cerebrovascular disease is outlined in Box 56.2.

KEY FACTS

✓ Most common cause of nontraumatic SAH—intracranial saccular aneurysm

✓ Onset of headache in SAH—characteristically sudden (thunderclap)

✓ Complications of SAH—intracranial arterial vasospasm, hyponatremia associated with a cerebral salt-wasting syndrome or the syndrome of inappropriate secretion of antidiuretic hormone, communicating hydrocephalus, seizures, and aneurysm rebleeding

✓ Outpouring of catecholamines in SAH—may cause myocardial damage and accompanying electrocardiographic abnormalities, pulmonary edema, and arrhythmias

✓ Arrhythmias in SAH—both supraventricular and ventricular and usually occur within hours or days after a moderate to severe SAH

57 Headache, Facial Pain, and "Dizziness"

AMAAL J. STARLING, MD

Headache and Facial Pain

Headache is considered to be a nearly universal experience. Approximately 98% of the population experiences some form of headache in a lifetime. The number of people with migraine worldwide is approximately 1 billion, and nearly 1 in every 4 US households has at least 1 family member who experiences migraine. Persons with headache disorders also present frequently to outpatient clinics; they are the reason for approximately 1 in every 10 consultations with a primary care physician. Migraine, in particular, poses a considerable societal and economic burden because it typically affects persons during the years associated with their peak productivity.

Distinguishing Primary Headache From Secondary Headache

The primary goal in the evaluation of any patient with headache should be to identify concerning features or red flags that may suggest the presence of an underlying and potentially sinister secondary cause of headache. A useful mnemonic to help remember red flags of headache features that warrant additional evaluation is *SNOOP4* (Box 57.1).

Thunderclap headache, or sudden-onset headache, is defined as a headache that is severe (typically described as the worst headache of one's life) and reaches maximal severity in less than 1 minute. Thunderclap headache is a medical emergency and warrants special attention and proper evaluation for underlying causes such as subarachnoid hemorrhage. Emergency computed tomography (CT) of the head is needed and should be performed as soon as possible because its sensitivity for detecting a subarachnoid hemorrhage decreases with time. If CT of the head is negative for relevant abnormalities, a lumbar puncture is indicated. A lumbar puncture helps to evaluate a possible subarachnoid hemorrhage or other causes of a thunderclap headache. If results from both CT of the head and lumbar puncture are unremarkable, additional investigations, including magnetic resonance imaging (MRI) of the brain and cerebrovascular imaging (either MRI or CT), are recommended because several possible underlying causes of thunderclap headache (many of which are vascular) may not be detected on routine noncontrast CT of the head (Box 57.2).

Key Definition

Thunderclap headache: *a headache that is severe (worst headache of one's life) and reaches maximal severity in <1 minute.*

The editors and authors acknowledge the contributions of Bert B. Vargas, MD, to the previous edition of this chapter.

Box 57.1 • *SNOOP4* Mnemonic: Red Flags for a Headache That May Have a Secondary Cause

Systemic disease or symptoms, including fevers, chills, mylagias, or weight loss

Neurologic signs or symptoms that are focal

Onset that is sudden or thunderclap

Older than 50 years at onset

Progressive worsening

Postural or positional

Precipitated by Valsalva maneuver or exertion

Previous headache history with new features

KEY FACTS

✓ Thunderclap headache—

- a medical emergency that warrants evaluation for subarachnoid hemorrhage
- emergency CT of the head is needed; if results are negative, lumbar puncture is done
- other imaging (MRI of the brain and cerebrovascular imaging) should strongly be considered because underlying causes of thunderclap headache (eg, vascular causes) may not be detected on routine noncontrast CT

Box 57.2 • Serious Causes of Headache That May Not Produce Abnormal Findings on Routine Computed Tomography of the Head

Vascular

- Reversible cerebral vasoconstriction syndrome (RCVS)
- Aneurysmal thrombosis or expansion
- Warning leak of aneurysm (sentinel bleed)
- Posterior reversible encephalopathy syndrome (PRES)
- Hypertensive crisis
- Cervical artery dissection
- Cerebral venous sinus thrombosis
- Ischemic stroke
- Pituitary apoplexy
- Giant cell or temporal arteritis

Nonvascular

- Meningitis
- Sinusitis (especially sphenoid sinusitis)
- Spontaneous intracranial hypotension (cerebrospinal fluid leaks)
- Third ventricle colloid cyst
- Pseudotumor cerebri
- Lesions around sella turcica
- Trigeminal or glossopharyngeal neuralgia
- Glaucoma
- Low intracranial pressure syndromes (cerebrospinal fluid leaks)

For patients older than 50 years with new-onset headache, evaluation to help rule out giant cell arteritis (GCA) should include laboratory investigations, including complete blood cell count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level. CRP is a more sensitive marker of inflammation than the ESR in GCA, and the CBC may show a normochromic anemia and thrombocytosis. These tests should be done even in the absence of classic features such as vision change, jaw claudication, palpable temporal artery abnormalities, and scalp allodynia. Temporal artery biopsy is the criterion standard for diagnosis and should be completed to confirm the diagnosis of GCA. However, diagnostic confirmation should not delay the initiation of treatment with corticosteroids because of the feared complication of ischemic optic neuropathy. If GCA is suspected, corticosteroid treatment should be initiated immediately to prevent ophthalmologic complications, and biopsy should be completed within 7 days. Rapid identification, diagnosis, and treatment of GCA can prevent blindness.

Differentiation and Treatment of Common Headache Disorders

Migraine

Although tension-type headache is the most common primary headache in the general population, it accounts for only 3% of the headache disorders evaluated in outpatient primary care clinics. Migraine is overwhelmingly the most common primary headache disorder evaluated in outpatient primary care clinics. Despite its relatively high prevalence (17% of women and 6% of men), migraine is underdiagnosed and therefore undertreated. Because migraine has been misdiagnosed for many patients as tension-type headache, sinus headache, or cluster headache, both patients and providers should be aware of the key differentiating features between primary headache disorders (Table 57.1). Diagnostic criteria for migraine, tension-type headache, and cluster headache, from the International Classification of Headache Disorders, 3rd edition (ICHD-3), are listed in Box 57.3.

Migraine is defined by multiple attacks of moderate to severe headache, often unilateral, which last several hours if untreated and are accompanied by photophobia, phonophobia, and osmophobia; nausea; a pounding quality to the headache; and an increase in intensity with light activity. However, a migraine attack can be bilateral and have a quality that feels like pressure. Approximately one-third of patients with migraine experience an aura before headache onset, most commonly described as visual, with flashing lights, jagged lines, or

Table 57.1 • Distinguishing Characteristics of Migraine, Cluster, and Tension-Type Headaches

Characteristic	Migraine	Cluster	Tension-Type
Duration	4-72 h	15-180 min	30 min to 7 d
Location	Unilateral (but may be bilateral)	Unilateral, orbital, or temporal (typically side-locked)	Typically bilateral
Pain quality	Moderate to severe	Excruciating	Mild to moderate
	Typically pulsating or throbbing		Typically pressing or tightening
Associated features	Must be associated with nausea or vomiting *or* with photophobia and phonophobia	Must be associated with ≥1 ipsilateral autonomic feature (eg, conjunctival injection or lacrimation, nasal congestion, or eyelid edema) *or* restlessness or agitation	Must be associated with no nausea or vomiting *and* with either photophobia or phonophobia

scintillating scotomas. Tension-type headaches can be severe but are most often mild to moderate, bilateral, and squeezing or tight in quality, and they lack other associated features that occur in migraine.

Migraine is separated into episodic or chronic migraine. A patient with *episodic migraine* has fewer than 15 migraine days per month, whereas a patient with *chronic migraine* has 15 or more headache days per month with at least 50% of the headaches having migraine features.

Therapy for migraine includes abortive medications to treat individual attacks and preventive medications to treat the underlying disease process and reduce the frequency, severity, and duration of attacks. Several medications with evidence-based efficacy are available to treat individual attacks both at home and in the acute-care setting. These include nonsteroidal anti-inflammatory drugs, acetaminophen, triptans, and dihydroergotamine (Table 57.2). Before they are used, several factors should be considered, including time to peak severity of headache (suggesting a need for medications with a rapid onset) and the presence of nausea or vomiting (suggesting a need for routes of administration other than oral).

To avoid medication overuse headache, measures should be taken to prevent the misuse or overuse of abortive medications, such as establishing limits to the frequency of use and providing preventive medications to decrease headache frequency. Triptans and ergotamines are vasoconstrictive and so are contraindicated in patients with coronary artery disease, uncontrolled hypertension, history of stroke or heart attack, or hemiplegic migraine.

Even though 40% of all patients with migraine may be eligible for treatment with preventive medications, only 13% actually receive it. Guidelines for the initiation of preventive treatment have been published by the American Academy of Family Physicians, the American College of Physicians, and the American Society of Internal Medicine with assistance from the American Headache Society and include the following scenarios:

1. More than 1 attack per week
2. Use of an abortive medication more than 2 days per week
3. Patients in whom abortive medications are contraindicated, not tolerated, or ineffective
4. Uncommon migraine conditions in which some abortive medications are contraindicated (ie, hemiplegic migraine)
5. Patient preference

Drugs frequently used for migraine prevention include antihypertensives, tricyclic antidepressants, and anticonvulsants. Current American Academy of Neurology recommendations are listed in Table 57.3. The only medications approved by the US Food and Drug Administration (FDA) for the prevention of episodic migraine are propranolol, timolol, divalproex sodium, and topiramate. Administration of onabotulinumtoxinA injections (155 units) every 12 weeks is the only FDA-approved preventive treatment for chronic migraine.

Despite the common understanding that valproic acid has substantial teratogenic potential, current research indicates that the use of topiramate also has the potential for serious and deleterious effects on embryologic and fetal development. The use of divalproex sodium or topiramate in women of childbearing potential should be accompanied with documented counseling about the potential risks and the use of birth control while taking these medications. Amitriptyline is useful for patients with either migraine or tension-type headache because the drug's common sedative effects can be effectively used at bedtime if patients have a coexisting complaint of disrupted sleep or insomnia. Among the antihypertensive medications, the level of evidence is strongest for β-blockers, but other blood pressure medications with weaker levels of evidence are commonly used and can be effective in select populations.

Several devices have been approved for migraine treatment. The transcutaneous supraorbital neurostimulator has been approved for migraine prevention, and the single-pulse transcranial magnetic stimulation device has been approved for both abortive and preventive treatment of migraine. In addition, a new class of medications, calcitonin gene–related peptide monoclonal antibodies, has undergone several successful phase 3 clinical trials. These medications are a novel, mechanism-based, disease-specific, targeted therapy for migraine prevention.

Box 57.3 • Diagnostic Criteria for Migraine Without Aura, Cluster Headache, and Tension-Type Headache

Migraine without aura

A. At least 5 attacks fulfilling criteria B-D

B. Attacks lasting 4-72 hours (untreated or unsuccessfully treated)

C. At least 2 of the following 4 characteristics:

1. Unilateral
2. Pulsating
3. Moderate or severe
4. Aggravation by or causing avoidance of routine physical activity

D. During headache, ≥1 of the following:

1. Nausea or vomiting
2. Photophobia and phonophobia

Cluster headache

A. At least 5 attacks fulfilling criteria B-D

B. Severe unilateral orbital, supraorbital, or temporal pain lasting 15-180 minutes (if untreated)

C. Either or both of the following:

1. At least 1 of the following signs or symptoms ipsilateral to the headache:
    a. Conjunctival injection or lacrimation
    b. Nasal congestion or rhinorrhea
    c. Eyelid edema
    d. Forehead and facial sweating
    e. Forehead and facial flushing
    f. Sensation of fullness in the ear
    g. Miosis or ptosis
2. A sense of restlessness or agitation

D. Frequency between 1 every other day and 8 per day for less than half the time when the disorder is active

Tension-type headache

A. At least 10 episodes occurring on <1 day per month on average and fulfilling criteria B-D

B. Lasting from 30 minutes to 7 days

C. At least 2 of the following 4 characteristics:

1. Bilateral
2. Pressing or tightening (nonpulsating) quality
3. Mild or moderate
4. Not aggravated by routine physical activity

D. Both of the following:

1. No nausea or vomiting
2. Either phonophobia *or* photophobia

Data from Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018 Jan;38(1):1-211.

KEY FACTS

- ✓ Strategies to prevent the overuse of abortive medications for migraine—limit the frequency of use and provide preventive medications to reduce headache frequency
- ✓ Triptans and ergotamines—vasoconstrictive and thus contraindicated in patients with migraine and coronary artery disease, uncontrolled hypertension, history of stroke or heart attack, or basilar or hemiplegic migraine
- ✓ Valproic acid and topiramate—may cause serious and deleterious effects on embryologic and fetal development
- ✓ Amitriptyline—useful for either migraine or chronic tension-type headache in patients with disrupted sleep or insomnia because it has sedative effects

Cluster Headache

Cluster headache is a subtype of a general class of headache disorders known as the trigeminal autonomic cephalgias (TACs). Unlike migraine, which predominantly affects women, the male to female ratio for cluster headache is 3 to 1. TACs have a side-locked unilateral distribution, are typically periorbital or retro-orbital, reach peak severity within minutes, and occur with at least 1 of several prominent autonomic features, including conjunctival injection, lacrimation, rhinorrhea, ptosis, miosis, facial flushing or sweating, eyelid or periorbital edema, or a sense of restlessness or agitation.

The TACs are subdivided by attack frequency and duration. The frequency of cluster headache ranges from 1 attack every other day to 8 in a day, with each attack lasting from 15 to 180 minutes. The episodic form of cluster headache often has a circadian rhythmicity and seasonal periodicity, and it may occur at or near a specific time in the day or night during certain seasons of the year. Chronic cluster headache is defined by attacks that occur for more than 1 year without remission or with periods of remission of less than 1 month.

The American Headache Society guidelines for the abortive and preventive treatment of cluster headache are summarized in Table 57.4. Treatments with the highest level of evidence for cluster attacks include subcutaneous sumatriptan, intranasal zolmitriptan, and high-flow oxygen (6-12 L/min) with a nonrebreather face mask.

Strong evidence is lacking to support any one preventive agent, besides suboccipital corticosteroid injections, for the treatment of cluster headache. First-line treatments typically include verapamil, melatonin, lithium, and brief courses of corticosteroids. Noninvasive vagal nerve stimulation has been approved by the FDA for treatment of attacks in patients with episodic cluster headache. Other treatments that seem to be promising

Table 57.2 • Evidence-Based Recommendations for Abortive Treatment of Migraine

Level A: Established Efficacy (≥2 Class I Trials)	Level B: Probably Effective (1 Class I or 2 Class II Studies)	Level C: Possibly Effective (1 Class II Study)	Level U: Inadequate or Conflicting Data
Acetaminophen (PO)	Chlorpromazine (IV)	Valproate (IV)	Celecoxib (PO)
Dihydroergotamine (IN, INH)	Droperidol (IV)	Ergotamine (PO)	Lidocaine (IV)
Aspirin (PO)	Metoclopramide (IV)	Phenazone (PO)	Hydrocortisone (IV)
Diclofenac (PO)	Prochlorperazine (IV, IM, PR)	Butorphanol (IM)	
Ibuprofen (PO)	Dihydroergotamine (IV, IM, SC)	Codeine (PO)	
Naproxen (PO)	Flurbiprofen (PO)	Meperidine (IM)	
Butorphanol (IN)	Ketoprofen (PO)	Methadone (IM)	
Almotriptan (PO)	Ketorolac (IV, IM)	Tramadol (IV)	
Eletriptan (PO)	Magnesium sulfate (IV, IM)	Dexamethasone (IV)	
Frovatriptan (PO)	Isometheptene (PO)	Butalbital (PO)	
Naratriptan (PO)	Codeine-acetaminophen (PO)	Lidocaine (IN)	
Rizatriptan (PO)	Tramadol-acetaminophen (PO)	Butalbital-acetaminophen-caffeine-codeine (PO)	
Sumatriptan (PO, SC, IN, patch)		Butalbital-acetaminophen-caffeine (PO)	
Zolmitriptan (IN, PO)			
Acetaminophen-aspirin-caffeine (PO)			
Sumatriptan-naproxen (PO)			

Abbreviations: IM, intramuscularly; IN, intranasally; INH, intranasal inhalation; IV, intravenously; PO, orally; PR, rectally; SC, subcutaneously.

but currently lack strong supportive evidence include sphenopalatine ganglion stimulation or blockade, pregabalin, short courses of corticosteroid, and both occipital and sphenopalatine ganglion neurostimulation.

Other TACs include *paroxysmal hemicrania* and *short-lasting unilateral neuralgiform headache with conjunctival injection and tearing* (SUNCT). Both have features identical to those of cluster headache, but paroxysmal hemicrania lasts 2 to 30 minutes, and SUNCT lasts 1 to 600 seconds. *Hemicrania continua* has a baseline level of side-locked pain with superimposed attacks of pain associated with unilateral cranial autonomic features. Paroxysmal hemicrania and hemicrania continua respond to indomethacin.

"Chronic Daily" Headache

Chronic daily headache is not a diagnosis but rather a description of symptoms. Primary headache disorders should never be diagnosed as *chronic daily* headache because numerous primary and secondary headaches can be chronic and occur daily. This point is especially important because correct diagnosis of the underlying headache disorder is key to the identification of appropriate treatment options and portends a better outcome for patients. The most common example is *chronic migraine*, which is defined by the ICHD-3 as headache for at least 15 days per month for more than 3 months with at least 8 headache days meeting the criteria for migraine with or without aura (Box 57.4).

A key differentiation between many chronic headache disorders is the duration of acute attacks (if untreated). A 4-hour time frame differentiates disorders such as chronic migraine and chronic tension-type headache from short-lasting headache disorders such as chronic cluster headache and chronic paroxysmal hemicrania (Box 57.5). Hemicrania continua is characterized by a continuous unilateral side-locked pain with superimposed attacks of no specific duration that are accompanied by any number of autonomic features of other TACs. New daily persistent headache may have features of either migraine or tension-type headache but is characterized by persistent daily headache

Table 57.3 • Evidence-Based Recommendations for the Preventive Treatment of Migraine

Level A: Established Efficacy (≥2 Class I Trials)	Level B: Probably Effective (1 Class I or 2 Class II Studies)	Level C: Possibly Effective (1 Class II Study)	Level U: Inadequate or Conflicting Data
Divalproex sodium Sodium valproate Topiramate Metoprolol Propranolol Timolol	Amitriptyline Venlafaxine Atenolol Nadolol	Lisinopril Candesartan Clonidine Guanfacine Carbamazepine Nebivolol Pindolol Cyproheptadine	Acetazolamide Acenocoumarol Coumadin Picotamide Fluvoxamine Fluoxetine Gabapentin Protriptyline Bisoprolol Nicardipine Nifedipine Nimodipine Verapamil Cyclandelate

of rather abrupt onset with no prior headache history. Affected patients frequently present with a history of a daily unremitting headache that began on a specific day.

Some medications effective for the prevention of episodic migraine are also used for the prevention of chronic migraine; however, the only FDA-approved preventive treatment of chronic migraine is onabotulinumtoxinA injections (155 units).

Potentially modifiable risk factors for the progression of episodic migraine to chronic migraine include frequency of attacks, obesity, caffeine and medication overuse, depression, and sleep disorders. In general, patients should be encouraged to limit their use of abortive medications to no more than 2 days per week, especially when using opioids or barbiturates, which have a higher likelihood of overuse, dependence, or abuse. Definitions for medication overuse are summarized in Box 57.6.

The management of daily or refractory headache should include transitional, abortive, and preventive treatments. Transitional treatments are designed to temporarily treat refractory pain and serve as a bridge to the long-term care plan. Transitional treatments may include hospitalization, outpatient infusion of abortive medications, brief courses of oral corticosteroid or nonsteroidal anti-inflammatory drugs given simultaneously with lifestyle modifications, trigger avoidance, and withdrawal of overused medications. Although many overused medications can be withdrawn abruptly, caution should be exercised with opioids and barbiturates, both of which may need to be withdrawn gradually.

TACs such as paroxysmal hemicrania and hemicrania continua often undergo rapid and full remission when patients receive therapeutic doses of indomethacin.

Trigeminal Neuralgia

Trigeminal neuralgia is characterized by sharp, electric-shock–like paroxysmal facial pain lasting seconds and occurring numerous times in a day, typically in association with tactile triggers, including touching the affected area, brushing one's teeth, drinking hot or cold liquids, chewing or swallowing, talking, or exposing the face to the wind. The pain can occur in any 1 of the 3 distributions of the trigeminal nerve, but it most commonly affects the second or third division with pain often radiating into the teeth. Although many cases of trigeminal neuralgia are idiopathic, vascular contact with or compression of the trigeminal nerve is a frequent underlying cause and can sometimes be corrected with microvascular decompression surgery in medically refractory cases. Trigeminal neuralgia is typically a unilateral phenomenon; if it occurs bilaterally, underlying secondary causes should be strongly considered.

Table 57.4 • Evidence-Based Recommendations for the Treatment of Cluster Headache

Type of Treatment	Level A: Established Efficacy (≥2 Class I Trials)	Level B: Probably Effective (1 Class I or 2 Class II Studies)	Level C: Possibly Effective (1 Class II Study)	Level U: Inadequate or Conflicting Data
Abortive	Sumatriptan (subcutaneous) Zolmitriptan (intranasal) Oxygen	Sumatriptan (intranasal) Zolmitriptan (oral) Sphenopalatine ganglion stimulation	Octreotide Cocaine-lidocaine (intranasal)	Dihydroergotamine (intranasal) Somatostatin Prednisone
Preventive	Suboccipital corticosteroid injection	Civamide	Melatonin Verapamil Lithium	Capsaicin Frovatriptan Nitrate tolerance Prednisone

Box 57.4 • Diagnostic Criteria for Chronic Migraine

A. Headache (tension-type–like or migraine-like) on ≥15 days per month for >3 months and fulfilling criteria B and C

B. Occurring in a patient who has had ≥5 attacks fulfilling criteria for migraine with or without aura

C. On ≥8 days per month for >3 months, fulfilling any of the following:

1. Criteria for migraine without aura
2. Criteria for migraine with aura
3. Believed by the patient to be migraine and relieved by a triptan or ergot

Data from Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018 Jan;38(1):1-211.

Box 57.5 • Differentiation of Common "Chronic Daily" Headaches by Duration of Attack

Short-lasting (<4 hours)

- Cluster headache
- Paroxysmal hemicrania
- SUNCT

Long-lasting (>4 hours)

- Chronic migraine
- Chronic tension-type headache
- New daily persistent headache
- Hemicrania continua

Abbreviation: SUNCT, short-lasting unilateral neuralgiform headache with conjunctival injection and tearing.

Box 57.6 • Diagnostic Criteria for Medication Overuse Headache

A. Headache present on ≥15 days per month

B. Regular overuse for >3 months of abortive medications as defined by the following:

1. Ergot, triptan, opioid, or butalbital analgesics for ≥10 days per month
2. Nonopioid analgesics for ≥15 days per month
3. All abortive drugs for ≥15 days per month

Data from Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018 Jan;38(1):1-211.

Medical treatment of trigeminal neuralgia includes carbamazepine, oxcarbazepine, phenytoin, baclofen, gabapentin, clonazepam, and lamotrigine. Surgical treatments include alcohol blocks, radiofrequency ablation of the gasserian ganglion (cranial nerve V), Gamma Knife (Elekta) radiosurgery, and microvascular decompression surgery.

KEY FACTS

✓ Abortive treatment of cluster headache with the highest level of evidence—subcutaneous sumatriptan, intranasal zolmitriptan, and high-flow oxygen with a nonrebreather face mask

✓ Prevention of chronic migraine—botulinum toxin injections are the only treatment approved by the FDA

✓ Trigeminal neuralgia—characterized by sharp, electric-shock–like paroxysmal facial pain lasting seconds and occurring numerous times a day

✓ Typical triggers of trigeminal neuralgia—touching the affected area, brushing one's teeth, drinking hot or cold liquids, chewing or swallowing, talking, or exposing the face to the wind

"Dizziness"

Dizziness is a nonspecific term that can describe any one of several subjective experiences, including light-headedness, vertigo, imbalance and unsteadiness, or ataxia. Because each of these complaints suggests different possible diagnoses and treatment options, a detailed history must be obtained and specific attention given to the patient's definition of *dizzy* and to specific details about timing, onset, duration, triggers, and the presence of neurologic signs or symptoms.

Accurate visual, vestibular, proprioceptive, tactile, and auditory perceptions are necessary for normal spatial orientation. These inputs are integrated in the brainstem and cerebral hemispheres. The outputs are the cortical, brainstem, and cerebellar motor systems. Impairment of any of these functions or their input, integration, or output causes a complaint of *dizziness* (ie, a sensation of altered orientation or space). Dizziness, vertigo, and dysequilibrium are common complaints. The results of diagnostic tests are often normal. Diagnosis depends mainly on the medical history, and physical examination findings are required in some cases. Vestibular tests rarely provide an exact diagnosis. The types of dizziness are listed in Box 57.7.

Presyncope and Light-headedness

Presyncope is frequently reported as feeling faint or light-headed and is rarely neurologic in origin. It commonly results

Box 57.7 • Types of Dizziness

- Vertigo
  - Peripheral
  - Central
- Presyncopal light-headedness
  - Orthostatic hypotension
  - Vasovagal attacks
  - Impaired cardiac output
  - Hyperventilation
- Psychophysiologic dizziness
  - Acute anxiety
  - Agoraphobia (fear and avoidance of being in public places)
  - Chronic anxiety
- Dysequilibrium
  - Lesions of basal ganglia, frontal lobes, and white matter
  - Hydrocephalus
  - Cerebellar dysfunction
- Ocular dizziness
  - High magnification and lens implant
  - Imbalance in extraocular muscles
  - Oscillopsia
- Multisensory dizziness
  - Physiologic dizziness
    - Motion sickness
    - Space sickness
    - Height vertigo

from pancerebral hypoperfusion and may indicate orthostatic hypotension, usually due to decreased blood volume, long-term use of antihypertensive drugs, or autonomic dysfunction. Other causes include vasovagal attacks, which are induced when emotions such as fear and anxiety activate medullary vasodepressor centers. Vasodepressor episodes can also be precipitated by acute visceral pain or sudden severe attacks of vertigo. Presyncopal light-headedness can be caused by impaired cardiac output or by hyperventilation. Chronic anxiety with associated hyperventilation is the most common cause of persistent presyncopal light-headedness in young patients, although postural orthostatic tachycardia syndrome (POTS) is also common in this population. In most persons, a moderate increase in respiratory rate can decrease the $Paco_2$ level to 25 mm Hg or less in a few minutes.

The 5 types of syncopal attacks that are especially common in elderly patients are listed in Box 57.8.

Box 57.8 • Syncopal Attacks Common Among Elderly Patients

Orthostatic—from multiple causes

Autonomic dysfunction—from peripheral (ie, postganglionic) or central (ie, preganglionic) involvement

Reflex—such as carotid sinus syncope or cough or micturition syncope

Vasovagal syncope—occurs less frequently in elderly patients than in young patients; however, the prognosis is worse for elderly patients, with about 16% of them having major morbidity or mortality within 6 months compared with less than 1% of patients younger than 30 years (common precipitating events in elderly patients include emotional stress, prolonged bed rest, prolonged standing, and painful stimuli)

Cardiogenic—from conditions such as arrhythmias or valvular disease

Vertigo

Vertigo is the sensation of movement (usually that of rotation) and the feeling of vertical or horizontal rotation of either the person or the environment around the person. Most patients report this as a “spinning” or “rotational” sensation. In contrast to vertigo, **dysequilibrium** is a feeling of unsteadiness or insecurity about the environment, without a rotatory sensation. Vertigo occurs when an imbalance exists, especially an acute imbalance, between the left and right vestibular systems. The sudden unilateral loss of vestibular function is dramatic; the patient complains of severe vertigo, nausea, and vomiting and is pale and diaphoretic. With acute vertigo, the patient also has problems with equilibrium and vision, often described as “blurred vision” or diplopia. Autonomic symptoms are common—sweating, pallor, nausea, and vomiting—and occasionally cause vasovagal syncope.

Key Definitions

Vertigo: *sensation of movement (usually that of rotation) and feeling of vertical or horizontal rotation or either the person or the environment around the person.*

Dysequilibrium: *feeling of unsteadiness or insecurity about the environment, without a rotatory sensation.*

Abrupt, complete, unilateral deafness and vertigo occur with viral involvement of the labyrinth or cranial nerve VIII (or both) and with ischemia of the inner ear. Patients who slowly lose vestibular function bilaterally, as may happen with the use of ototoxic drugs, often do not complain of vertigo but have oscillopsia with head movements and instability with walking. Even if unilateral vestibular loss occurs slowly (eg, as in acoustic neuroma), patients usually do not complain of vertigo; they typically present with unilateral hearing loss and tinnitus. Vertigo frequently occurs in episodes. Common vestibular disorders with a genetic predisposition include migraine, Meniere disease, otosclerosis, neurofibromatosis, and spinocerebellar degeneration.

Meniere Disease

Fluctuating vertigo, sensorineural hearing loss, aural fullness, and tinnitus are characteristic of Meniere disease. The disease has been linked to endolymphatic hydrops but is now thought to be an epiphenomenon associated with various disorders of the inner ear. In addition to a history and physical examination, an audiogram should be obtained. Brain imaging, preferably MRI of the brain, will help rule out secondary causes, including posterior fossa lesions that may lead to progressive hearing loss and vertigo. Acute attacks are treated symptomatically with antiemetics. No preventive options have strong levels of evidence. However, common recommendations include salt restriction (daily sodium intake of <2 g) and diuretics.

Benign Positional Vertigo

Benign positional vertigo is the most common cause of vertigo. Symptoms include brief episodes of vertigo that usually last from 30 seconds to 1 to 2 minutes and are specifically associated with positional change (eg, turning over in bed, getting in or out of bed, bending over and straightening up, and extending the neck to look up). Typically, the underlying cause is displaced otoliths in 1 of the semicircular canals disrupting the normal flow of endolymphatic fluid and creating a false sense of motion. In about half the patients who do not have benign positional vertigo, no cause is found. For the other half, the most common causes are posttraumatic and postviral neurolabyrinthitis.

Typically, bouts of benign positional vertigo are intermixed with variable periods of remission. Although episodes of vertigo are typically short-lasting, patients may complain of more prolonged nonspecific dizziness that lasts hours to days after a flurry of episodes (eg, light-headedness or a swimming sensation associated with nausea). Management includes reassurance, positional exercises (ie, vestibular exercises), and canalith repositioning maneuvers such as the Epley maneuver. Although pharmacologic treatment is typically of little value, meclizine and promethazine are frequently used and may provide some benefit. Rarely, in intractable cases, surgical treatment (section of the ampullary nerve) may be needed.

Vestibular Migraine

Vestibular migraine is a common cause of episodic vestibular symptoms. The ICHD-3 criteria require 5 or more episodes of moderate to severe recurrent vestibular symptoms that last from 5 minutes to 72 hours. At least 50% of the episodes should be associated with at least 1 of these 3 features: 1) headache with features of migraine, 2) photophobia and phonophobia, and 3) visual aura. Whether the underlying pathophysiology of vestibular migraine is different from that of migraine is unclear. The abortive and preventive treatment of vestibular migraine is generally the same as for migraine. Some data support the use of calcium channel blockers such as flunarizine or cinnarizine. In addition to pharmacotherapy, the discontinuation of caffeine and the use of vestibular exercises have been beneficial for patients.

Cerebellar Lesions

Vertigo of central nervous system origin can be caused by acute cerebellar lesions (hemorrhages or infarcts) or acute brainstem lesions (especially the lateral medullary syndrome [also called Wallenberg syndrome]). Vertebrobasilar arterial disease can also cause brief transient episodes of vertigo, but it rarely occurs without other focal or localizing neurologic signs and symptoms such as dysarthria, dysphagia, diplopia, facial numbness, crossed syndromes, hemiparesis or alternating hemiparesis, ataxia, and visual field defects.

Dysequilibrium

Patients who slowly lose vestibular function on 1 side, as with an acoustic neuroma, usually do not have vertigo but often describe a vague feeling of imbalance and unsteadiness on their feet. Dysequilibrium may be a presenting symptom when lesions involve motor centers of the basal ganglia and frontal lobe (eg, Parkinson disease, hydrocephalus, and multiple lacunar infarctions). The broad-based ataxic gait of persons with cerebellar disorders is readily distinguished from milder gait disorders that occur with vestibular or sensory loss or with senile gait.

Persistent Postural-Perceptual Dizziness

Persistent postural-perceptual dizziness (PPPD) is a newly defined syndrome unifying the prior diagnoses of chronic subjective dizziness, phobic postural vertigo, and other related disorders. The diagnosis relies heavily on patient history. Unsteadiness, nonrotational vertigo, and dysequilibrium are characteristic features. Typically, patients have had a provocative, acute event, such as an episode of benign paroxysmal positional vertigo, vestibular neuritis, or vestibular migraine attack. Symptom exacerbation or triggers include active or passive movement, upright posture, or complicated visual stimuli. Management of PPPD is individualized and includes vestibular exercises, pharmacotherapy, and cognitive behavioral therapy. The goal of vestibular exercises is to habituate an abnormal reflexive response to visually distressing stimuli and reduce visual hypersensitivity to complicated and moving stimuli. Selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors have been effective for some patients in open-label trials, although no randomized controlled trials have been completed.

Multifactorial Dizziness and Imbalance

Multifactorial dizziness and imbalance are common in elderly patients and in patients with systemic disorders such as diabetes mellitus. A typical combination includes, for example, mild peripheral neuropathy that causes diminished touch and proprioceptive input, decreased visual acuity, impaired hearing, and decreased baroreceptor function. In affected patients, an added vestibular impairment, as from an ototoxic drug, can be devastating.

The resulting sensation of dizziness and imbalance is usually present only when the patient walks or moves and not when the patient is supine or seated. The patient feels insecure with gait and motion and so is usually helped by walking close to a wall, using a cane, or holding on to another person. Drugs should not be prescribed for this disorder. Instead, a cane or walker is used to improve support and to increase somatosensory signals. The patient's medications should be thoroughly reviewed, and laboratory investigations should be considered when peripheral neuropathy is thought to be contributory. Common laboratory investigations include electromyography; determination of levels of vitamin B_{12}, folate, thyroid-stimulating hormone, and hemoglobin A_{1c} or a 2-hour glucose tolerance test; and serum protein electrophoresis.

KEY FACTS

✓ Meniere disease—fluctuating vertigo, hearing loss, aural fullness, and tinnitus

✓ Multifactorial dizziness and imbalance—common in elderly patients and patients with systemic disorders such as diabetes mellitus

✓ Sensation of dizziness and imbalance—usually present only when a patient walks or moves and not when supine or seated

✓ Multifactorial dizziness and imbalance—use of a cane or walker improves support and increases somatosensory signals

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Inflammatory and Autoimmune Central Nervous System Diseases and the Neurology of Sepsis

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Inflammatory Central Nervous System Diseases

Multiple Sclerosis

The most common inflammatory demyelinating disease of the central nervous system (CNS) is multiple sclerosis (MS), a disabling disorder that affects predominantly young adults between 20 and 50 years old. It affects women twice as often as men. MS has a complex immunopathogenesis, a variable prognosis, and an unpredictable course. Polygenic and environmental (vitamin D deficiency and possibly viral) factors probably have a substantial effect on susceptibility to MS. The disease attacks white matter and (in both early and late stages) axons of the cerebral hemispheres, brainstem, cerebellum, spinal cord, and optic nerve. Most patients (80%-85%) present with relapsing-remitting symptoms. In about 15% of patients, the disease is progressive from onset (primary progressive). Over time, in 70% of patients with the relapsing-remitting form, secondary progressive MS develops. A minority (usually older patients) have a primary progressive course without a preceding relapsing course.

Symptoms reflect multiple white matter lesions disseminated in space and time. Typical syndromes include optic neuritis, myelitis, brainstem syndromes, and paroxysmal attacks. Optic neuritis manifests with unilateral visual loss frequently associated with eye pain on movement. Myelitis manifests with sensory symptoms, including a bandlike sensation in the abdomen and chest, spastic weakness of the limbs, and bladder and bowel dysfunction. Other typical symptoms include diplopia (due to internuclear ophthalmoplegia) and ataxia. Paroxysmal symptoms, including trigeminal neuralgia and hemifacial spasm, in a young patient should increase awareness for MS. Other important symptoms are memory and cognitive dysfunction and depression. Associated features that suggest MS include excessive unexplained fatigue and exacerbation of symptoms on exposure to heat.

The diagnosis is primarily based on clinical and magnetic resonance imaging (MRI) data that show lesions disseminated in space and time. Abnormalities on MRI are most helpful and include multifocal lesions of various ages in the periventricular white matter, corpus callosum, brainstem, cerebellum, and spinal cord. Gadolinium-enhanced lesions are presumed to be active lesions of inflammatory demyelination. In patients with clinically isolated syndromes, such as optic neuritis, myelopathy, or brainstem syndrome, abnormal MRI findings are a strong predictor of the eventual clinical diagnosis of MS in the next 5 years. Cerebrospinal fluid (CSF) findings include CSF-restricted oligoclonal bands, increased immunoglobulin (Ig)G synthesis or synthesis rate, and moderate lymphocytic pleocytosis (<50 mononuclear cells/mcL). Visual and somatosensory evoked potential studies are less helpful.

Many other disorders mimic MS and should be considered when patients have atypical findings. Important examples include vasculitis, infections (eg, human immunodeficiency virus infection or Lyme disease), paraneoplastic disorders, neurosarcoidosis, systemic lupus erythematosus, Behçet syndrome, and lymphoma.

Predictors associated with a more favorable long-term course of MS include age younger than 40 years at onset, female sex, optic neuritis or isolated sensory symptoms as the first clinical manifestation, and relatively infrequent attacks. Prognostic factors associated with a poor outcome include age older than

40 years at onset, male sex, cerebellar or pyramidal tract findings at initial presentation, relatively frequent attacks during the first 2 years, incomplete remissions, and a chronically progressive course. However, no single clinical variable is sufficient to predict the course or outcome of this disease. Some evidence indicates that a subset of patients with MS has very benign disease; hence, not every patient with MS must receive long-term treatment.

The recommended therapy for acute exacerbations of MS is a 3- to 5-day course of a high dose of intravenous methylprednisolone (1.0 g daily). Severe or steroid-unresponsive exacerbations are treated with plasma exchange (5-7 exchanges administered on an alternate-day schedule for 10-14 days).

Traditional immunomodulatory agents are used to prevent relapses and are administered subcutaneously or intramuscularly. In clinical trials, reduction in the relapse rate with these drugs has been approximately 33% for interferon beta-1a, interferon beta-1b, and glatiramer acetate. Newer oral agents, including fingolimod, dimethyl fumarate, and teriflunomide, decrease the relapse rate to a level that is comparable to the relapse rate with traditional injectable interferon therapies. In severe or refractory disease, intravenous natalizumab can decrease the relapse rate by 70%, but it can cause untreatable CNS infection (progressive multifocal leukoencephalopathy) in patients who have JC virus antibody in their serum.

Intravenous monoclonal antibody therapies include ocrelizumab (against the B-lymphocyte CD20 antigen; approved for primary progressive MS); alemtuzumab (against the mature lymphocyte CD52 antigen; approved for treatment-resistant relapsing-remitting MS); and daclizumab (against the interleukin 2 receptor; approved for relapsing-remitting MS).

Important adverse effects include infusion reactions (all intravenous therapies), autoimmunity (alemtuzumab), depression (interferon therapies), injection site reactions (interferons and glatiramer acetate), flushing and gastrointestinal tract symptoms (dimethyl fumarate and teriflunomide), heart block (fingolimod), macular edema (fingolimod), elevated liver function test results (interferon therapies, fingolimod, and teriflunomide), and life-threatening opportunistic infection (natalizumab and fingolimod).

General periodic monitoring includes liver function tests and complete blood cell counts; in addition, patients receiving natalizumab should be monitored for JC virus antibody seroconversion (from negative to positive). In 5% to 30% of patients receiving interferon beta, neutralizing antibodies develop and block its effects.

Several drugs are used to treat specific symptoms of MS. Trigeminal neuralgia, flexor spasms, and other paroxysmal symptoms respond to carbamazepine, and spasticity responds to baclofen and tizanidine. Fatigue, a disabling symptom of MS, occasionally responds to amantadine, modafinil, or stimulants.

KEY FACTS

- ✓ MS—most common inflammatory demyelinating disease of the CNS
- ✓ Most patients with MS (80%-85%) present with relapsing-remitting symptoms
- ✓ Typical syndromes in MS—optic neuritis, myelitis, brainstem syndromes, and paroxysmal attacks
- ✓ Diagnosis of MS—primarily based on clinical and MRI data that show lesions disseminated in space and time
- ✓ CSF findings in MS—CSF-restricted oligoclonal bands, increased IgG synthesis or synthesis rate, and moderate lymphocytic pleocytosis (<50 mononuclear cells/mcL)
- ✓ Recommended therapy for acute exacerbations of MS—3- to 5-day course of a high dose of intravenous methylprednisolone (1.0 g daily); severe or steroid-unresponsive exacerbations are treated with plasma exchange

Monophasic Inflammatory Disorders

Some patients have single-episode acute demyelinating events that do not evolve into MS. Some of these events are hypothesized to occur as parainfectious inflammatory disorders. They can be single episodes of optic neuritis or transverse myelitis. These disorders are usually mild and self-limiting. However, acute disseminated encephalomyelitis usually presents in children or young adults with widespread neurologic dysfunction and diffuse inflammatory-appearing lesions on brain and spinal cord imaging. The treatment of all these disorders described is the same as that of acute attacks of MS: corticosteroids, in the first instance, and plasma exchange, if necessary. Myelin oligodendrocyte glycoprotein (MOG)-IgG1 has emerged as a biomarker of steroid-responsive monophasic or recurrent autoimmune optic neuritis, myelitis, and acute disseminated encephalomyelitis (ADEM).

Other Inflammatory CNS Disorders

Neurosarcoidosis is likely the second most common chronic CNS inflammatory disorder after MS. Neurologic manifestations are protean, and it is often referred to as the "great mimicker" of other common CNS disorders, including MS and tumors. MRI shows unifocal or multifocal inflammatory lesions of both the parenchyma and the pial meninges. Clinical examination and imaging of nonneurologic organs can raise suspicion for a multisystem disorder and provide a biopsy site more accessible than brain from which to obtain a tissue diagnosis. Other, rare inflammatory CNS disorders include Langerhans cell histiocytosis, Erdheim-Chester disease, and Susac syndrome.

Autoimmune CNS Diseases

Paraneoplastic and Other Autoimmune Disorders

Broadly speaking, a paraneoplastic disorder occurs because of the remote effects of malignancy, rather than because of direct tumor invasion. Paraneoplastic neurologic disorders come about because of vigorous immune responses directed against antigens expressed in tumors. The vigor of the immune response usually ensures that a neoplasm is confined to the primary organ and regional lymph nodes. The neurologic presentation is often the first clue to the existence, or recurrence, of cancer. Autoimmune neurologic disorders may also arise in idiopathic autoimmune contexts (eg, stiff-person syndrome, Lambert-Eaton syndrome, and neuropsychiatric lupus) and in parainfectious autoimmune contexts (eg, anti-NMDA [*N*-methyl-D-aspartate] receptor encephalitis occurring after herpes simplex encephalitis).

The most common neural antibodies, common neurologic findings, and oncologic associations of autoimmune neurologic disorders are listed in Table 58.1. Neurologic presentations are protean and may affect any level of the neuraxis. Symptom onset is usually subacute, and progression is rapid. In any individual patient, the neurologic presentation may be a classic unifocal disorder (eg, pure limbic encephalitis in a patient with voltage-gated potassium channel complex antibody) or multifocal disorder (eg, stiff-person syndrome and ataxia in a patient with glutamic acid decarboxylase [GAD]65 antibody positivity). Nonneural antibodies, such as markers of lupus and thyroid antibodies, may be clues to an autoimmune diagnosis. In addition to IgG antibody markers, testing that aids confirmation of an autoimmune diagnosis includes imaging, neurophysiologic, and CSF evaluations. An autoimmune neurologic diagnosis is supported by 1 or more of the following: increased CSF protein, white cell count, IgG index, IgG synthesis rate, and oligoclonal bands. The search for cancer may be aided by detection of a specific antibody. CSF testing for paraneoplastic antibodies may complement serologic testing when serologic testing has been negative.

The primary therapy for autoimmune neurologic disorders is treatment of the cancer in the standard way (with surgery, chemotherapy, or radiotherapy or more than 1 of these). One or more immunotherapies (corticosteroids, intravenous immunoglobulin, plasma exchange, cyclophosphamide) may provide additional neurologic improvements when cancer remission has been achieved, although responses vary.

Table 58.1 • Examples of Autoimmune Neurologic Disorders

Antibody	Oncologic Association	Neurologic Presentation
Amphiphysin IgG	Small cell carcinoma, breast adenocarcinoma	Encephalitis, stiff-person syndrome, myelopathy, neuropathy
ANNA-1 (anti-Hu)	Small cell carcinoma	Encephalitis, brainstem encephalitis, autonomic neuropathies, peripheral neuropathies
ANNA-2 (anti-Ri)	Small cell carcinoma, breast adenocarcinoma	Encephalitis, brainstem encephalitis, myelopathy, neuropathy
Calcium channels (P/Q- and N-types)	Small cell carcinoma, or nonparaneoplastic	Lambert-Eaton myasthenic syndrome, encephalitis, myelopathy
GAD65	Usually no cancer found	Stiff-person syndrome, ataxia, encephalitis, parkinsonism, myelopathy
Ma1, Ma2	Testicular (Ma2 only); breast, colon, testicular (Ma1 and Ma2 together)	Encephalitis, brainstem encephalitis
Muscle AChR	Thymoma or nonparaneoplastic	Myasthenia gravis
Neuronal AChR	Adenocarcinomas, thymoma in 30%; nonparaneoplastic in 70%	Autoimmune dysautonomia
NMDA receptor	Ovarian teratoma (50% of patients)	Anxiety, psychosis, seizures, encephalitis, dyskinesias
PCA-1 (anti-Yo)	Ovarian or other gynecologic tract adenocarcinoma, breast adenocarcinoma	Cerebellar ataxia, brainstem encephalitis, myelopathy, neuropathies
PCA-Tr (DNER-IgG)	Hodgkin lymphoma	Cerebellar ataxia
VGKC complex	Various in about 20%, or nonparaneoplastic	Limbic encephalitis, amnestic syndrome, executive dysfunction, personality change, disinhibition, hypothalamic disorder, brainstem encephalitis, ataxia, extrapyramidal disorders, myoclonus, peripheral and autonomic neuropathy

Abbreviations: AChR, acetylcholine receptor; ANNA, antineuronal nuclear antibody; DNER, delta/notch-like epidermal growth factor; GAD65, 65 kDa isoform of glutamic acid decarboxylase; Ig, immunoglobulin; NMDA, *N*-methyl-D-aspartate; PCA, Purkinje cell cytoplasmic antibody; Tr, Trotter (named after John Trotter, who first described this antibody); VGKC, voltage-gated potassium channel.

Neuromyelitis Optica

Neuromyelitis optica, an example of an autoimmune CNS disorder, is a recurrent, severe demyelinating disease that may mimic MS. In contrast to MS, the pathophysiology of this disorder is relatively well understood. Antibody targets the CNS-predominant water channel, aquaporin 4, resulting in a cascade of inflammatory events leading to attacks of neurologic symptoms. The diagnosis is based on the following: 1) presence of severe optic neuritis or transverse myelitis, or both; 2) MRI evidence of contiguous spinal cord lesions spanning more than 3 vertebral segments; and 3) presence of neuromyelitis optica–IgG (aquaporin 4–IgG) in serum. Encephalitis occasionally occurs, most often in children. In 12% of patients, intractable vomiting occurs because of brainstem encephalitis. In neuromyelitis optica, unlike in MS, the CSF often shows polynuclear pleocytosis (>50 cells/mcL) and usually an absence of oligoclonal bands. Exacerbations may respond to intravenous methylprednisolone or plasma exchange. The presence of neuromyelitis optica–IgG antibodies indicates risk of recurrence and warrants long-term immunosuppression with azathioprine, mycophenolate, or rituximab.

Key Definition

Neuromyelitis optica: *an autoimmune CNS disorder; a recurrent, severe demyelinating disease that may mimic MS.*

Neurology of Sepsis

The nervous system is commonly affected in sepsis syndrome. The neurologic conditions encountered are septic encephalopathy, critical illness polyneuropathy or myopathy (or both), cachexia, and panfascicular muscle necrosis. Neurologic complications also occur in intensive care units for critical medical illness. These complications include metabolic encephalopathy, seizures, hypoxic-ischemic encephalopathy, and stroke.

Septic Encephalopathy

Septic encephalopathy is brain dysfunction in association with systemic infection without overt infection of the brain or meninges. Early encephalopathy often begins before failure of other organs and is not due to single or multiple organ failure. Endotoxin does not cross the blood-brain barrier and so probably does not directly affect adult brains. Cytokines, important components of sepsis syndrome, may contribute to encephalopathy. Gegenhalten, or paratonic rigidity occurs in more than 50% of patients, and tremor, asterixis, and multifocal myoclonus occur in about 25%. Seizures and focal neurologic signs are rare.

Key Definition

Septic encephalopathy: *brain dysfunction in association with systemic infection without overt infection of the brain or meninges.*

Electroencephalography is a sensitive indicator of encephalopathy. The mildest abnormality is diffuse excessive low-voltage theta activity (4-7 Hz). The next level of severity is intermittent rhythmic delta activity (<4 Hz). As the condition worsens, delta activity becomes arrhythmic and continuous. Typical triphasic waves occur in severe cases, especially in hepatic failure. In these cases, MRI and computed tomography of the brain may be normal.

Critical Illness Polyneuropathy and Myopathy

Critical illness polyneuropathy occurs in 70% of patients with sepsis and multiple organ failure. These patients often present an unexplained difficulty in being weaned from mechanical ventilation. Nerve biopsy specimens show primary axonal degeneration of motor and sensory fibers without inflammation. Critical illness myopathy is also recognized in patients with sepsis. Similarly, biopsy results show degenerative changes without inflammation. Most patients have findings of both myopathy and neuropathy. Recovery is satisfactory if the patient survives sepsis and multiple organ failure. Treatment is supportive care and rehabilitation.

KEY FACTS

- ✓ Primary therapy for autoimmune neurologic disorders—treatment of the cancer in the standard way
- ✓ Diagnosis of neuromyelitis optica—based on 1) presence of severe optic neuritis or transverse myelitis, or both; 2) MRI evidence of contiguous spinal cord lesions spanning >3 vertebral segments; and 3) presence of neuromyelitis optica–IgG (aquaporin 4–IgG) in serum
- ✓ Critical illness polyneuropathy—occurs in 70% of patients with sepsis and multiple organ failure
- ✓ Recovery from critical illness polyneuropathy and myopathy is satisfactory if the patient survives sepsis and multiple organ failure; treatment is supportive care and rehabilitation

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Movement Disorders

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Movement disorders are common in adult clinical practice. An important first step in evaluation and management of these disorders is identification of a potentially reversible cause, most commonly a medication effect. All patients younger than 50 years presenting with any type of movement disorder should be evaluated for Wilson disease.

Tremor

Tremor is an oscillatory rhythmic movement that may occur in isolation, as in essential tremor, or as part of another condition such as Parkinson disease or cerebellar disorders. *Rest tremor* is observed with the limb fully relaxed and supported, with the arms lying in the lap or hanging at the side (eg, while walking) or the legs hanging over the examining table. The most common cause of rest tremor is Parkinson disease. Several types of action tremor are triggered by muscle contraction. *Postural tremor* occurs when the body part is held in a sustained posture (eg, arms held outstretched or head held erect). Postural tremor includes exaggerated physiologic tremor, essential tremor, tremor induced by drugs (eg, methylxanthines, β-adrenergic agonists, lithium, and amiodarone) or toxic-metabolic conditions (eg, stimulant overuse or alcohol withdrawal), and neuropathic tremor. *Intention tremor* is worsened with action, as in finger-to-nose testing, especially the terminal part of the movement. This type of tremor occurs with diseases of the cerebellum or its connections. *Task-related tremor* occurs during specific tasks and includes primary writing tremor (which may occur in association with writer's cramp) and orthostatic tremor, which occurs only when a patient is standing.

Essential Tremor

Essential tremor is the most common movement disorder and can be differentiated from Parkinson disease tremor (Table 59.1). It is most common in middle and older age. Patients often have a positive family history. The hands are most frequently affected, with both postural and intention tremor, followed by the head and voice. Head tremor can be either horizontal ("no-no") or vertical ("yes-yes"). Head tremor almost never occurs in Parkinson disease, although patients with Parkinson disease may have tremor of the mouth, lips, tongue, and jaw. The legs and trunk (affected in orthostatic tremor) are affected less frequently in essential tremor. Essential tremor is slowly progressive, and its pathophysiologic mechanism is not known.

Essential tremor typically improves with alcohol, but alcohol can also improve other forms of tremor. First-line medications are propranolol (40 mg daily, up to 320 mg daily) (or other β-blockers) and primidone (25-250 mg at bedtime). Second-line drugs are clonazepam, gabapentin, and topiramate. Deep brain stimulation of the thalamus is effective for all types of medication-refractory tremor with functional disability.

Parkinson Disease

Patients with Parkinson disease present with tremor (the initial symptom in 50%-70%, but 15% never have tremor), rigidity, or bradykinesia. The gait is unsteady, slow, and shuffling. Decreased blink rate, lack of facial expression, small handwriting, and asymptomatic orthostatic hypotension are also common. Parkinson disease includes motor manifestations (Box 59.1) and nonmotor manifestations (Box 59.2). Typically

Table 59.1 • Differential Diagnosis of Tremor

Feature	Parkinson Disease	Essential Tremor
Tremor type and frequency	Rest >> postural; 3-5 Hz	Postural, kinetic; 8-12 Hz
Affected by tremor	Hands, legs, chin, jaw	Hands, head, voice
Rigidity and bradykinesia	Yes	No
Family history	15%	60%
Alcohol response	Inconsistent	Consistent
Therapy	Levodopa, dopamine agonists, anticholinergics	Propranolol, primidone, gabapentin (botulinum toxin for head tremor)
Surgical treatment	Subthalamic, globus pallidus interna stimulation	Thalamic (Vim) stimulation

Abbreviations: Vim, subnucleus ventralis intermedius; >>, much greater than.

nonmotor manifestations, such as anosmia, rapid eye movement (REM) sleep behavior disorder (RBD) and constipation, precede the development of motor symptoms for many years. The classic motor manifestations of Parkinson disease are rest tremor, muscle stiffness (rigidity), and slowness of movement (bradykinesia), which typically start asymmetrically and respond to levodopa therapy. Late motor manifestations, including difficulty swallowing, postural instability, and freezing of gait, are much less responsive to treatment. At late stages of Parkinson disease after prolonged dopamine replacement therapy, patients have motor fluctuations or dyskinesia (chorea-like movements of the limbs, trunk, or head). Eventually symptoms develop that do not respond to levodopa, including falls and cognitive impairment.

The differential diagnosis of Parkinson disease includes disorders caused by drugs (Box 59.3), toxins (eg, carbon monoxide and manganese), neurometabolic disorders (particularly

Box 59.1 • Motor Manifestations of Parkinson Disease

- Early manifestations (typically asymmetric in onset and responsive to levodopa)
  - Rest tremor
  - Rigidity
  - Bradykinesia
- Late manifestations (less responsive to levodopa)
  - Gait and postural instability
  - Dysphagia
  - Motor fluctuations (wearing-off and on-off phenomena)
  - Levodopa-induced dyskinesia

Box 59.2 • Nonmotor Manifestations of Parkinson Disease

- Autonomic
  - Constipation[a]
  - Orthostatic hypotension
  - Bladder dysfunction
- Sleep disorders
  - Excessive diurnal somnolence
  - Insomnia
  - RBD[a]
- Cognitive symptoms
  - Depression[a]
  - Anxiety
  - Apathy
  - Hallucinations
  - Mild cognitive impairment, dementia
- Sensory symptoms
  - Impaired olfaction[a]

Abbreviation: RBD, rapid eye movement (REM) sleep behavior disorder.

[a] May precede the diagnosis of disease.

Box 59.3 • Drugs That Induce Parkinsonism or Tremor

- Antagonists of dopamine D_2 receptors
  - Neuroleptics (eg, haloperidol, risperidone, reserpine, aripiprazole)
- Antiemetics (metoclopramide, prochlorperazine)
- Other psychiatric drugs
  - Selective serotonin reuptake inhibitors
  - Tricyclics
  - Lithium
- Cardiovascular drugs
  - Amiodarone
  - Calcium channel blockers (flunarizine)
- Anticonvulsants
  - Valproate
- Others
  - Cyclosporine
  - Metronidazole
  - Caffeine and other methylxanthines
  - α-Adrenergic agonist
  - Thyroxine
  - Prednisone

Table 59.2 • Differential Diagnosis of Atypical Parkinsonian Syndromes

Manifestation	Suspect
Poor response to levodopa	Any atypical parkinsonian syndrome (MSA and PSP may respond)
Early falls	PSP or MSA
Severe OH, urologic symptoms, stridor, or RBD	MSA
Cerebellar signs	MSA or spinocerebellar degeneration
Corticospinal tract signs	MSA or corticobasal degeneration
Vertical gaze palsy	PSP
Asymmetric apraxia	Corticobasal degeneration
Early dementia	Lewy body dementia Creutzfeldt-Jakob disease

Abbreviations: MSA, multiple system atrophy; OH, orthostatic hypotension; PSP, progressive supranuclear palsy; RBD, rapid eye movement (REM) sleep behavior disorder.

Wilson disease in patients younger than 50 years), and other neurodegenerative disorders in which parkinsonism is a prominent feature (atypical parkinsonian syndromes) (Table 59.2). Manifestations that suggest a disorder other than Parkinson disease (red flags) include a lack of response to levodopa, early postural instability with falls, orthostatic hypotension or urinary incontinence, cerebellar findings (ataxia), corticospinal signs (increased deep tendon reflexes, spasticity, or extensor plantar response), and early dementia.

Treatment of the motor manifestations of Parkinson disease is summarized in Table 59.3. The initial treatment options include levodopa in combination with carbidopa or dopamine agonists. Anticholinergic agents can suppress tremor but are rarely used now and should be avoided in patients older than 65 years because of frequent adverse effects, such as memory loss, delirium, urinary hesitancy, and blurred vision. Patients with disabling symptoms should receive carbidopa-levodopa. The initial dosage is a 25/100 tablet (25 mg carbidopa/100 mg levodopa) by mouth 3 times daily on an empty stomach. Starting with dopamine agonists reduces the risk of motor complications compared with long-term levodopa therapy, but these agents are less efficacious than levodopa. Dopamine agonists include pramipexole and ropinirole. The main adverse effects of levodopa and dopamine agonists are nausea, orthostatic hypotension, and hallucinations. All can cause unpredictable daytime sleepiness. An important adverse effect of dopamine agonists is impulse control disorders, manifested as compulsive gambling, compulsive shopping, or pathologic hypersexuality. Patients and their families should be counseled about these problems before initiation of dopamine agonist therapy.

Selegiline or rasagiline (monoamine oxidase inhibitors type B) may give mild symptomatic relief in early Parkinson disease and delay the need for levodopa therapy. Adverse effects include nausea, hallucinations, confusion, dyskinesias, and orthostatic hypotension.

Table 59.3 • Management of Motor Manifestations of Parkinson Disease

Therapy[a]	Indications	Complications and Adverse Effects
Carbidopa-levodopa (25/100[b], 50/200[c])	Most efficacious treatment Give early if patients have marked impairment	Nausea, vomiting, OH Motor fluctuations with long-term treatment
Carbidopa-levodopa (23.75/95, 36.25/145, 48.75/195, 61.25/245)[d]	Motor fluctuations in patients taking immediate-release levodopa	Nausea, vomiting, OH
Dopaminergic agonists Pramipexole Ropinirole Rotigotine	Early use in young patients, either alone or associated with small dose of levodopa Motor fluctuations in patients taking levodopa	Nausea, vomiting, OH More likely than levodopa to produce excessive diurnal somnolence, impulse control disorder (eg, gambling), hallucinations, or peripheral edema
COMT inhibitors Entacapone	Prolong the duration of action of levodopa in patients with wearing-off effect	Diarrhea
MAO-B inhibitors Selegiline Rasagiline	Delay the need to start levodopa therapy May be neuroprotective	Insomnia (with selegiline); nausea, hallucinations, confusion, dyskinesias, OH
Amantadine	Adjuvant treatment in patients with levodopa-induced dyskinesia	Dizziness, livedo reticularis, edema
Carbidopa-levodopa enteral suspension (carbidopa 4.63 mg, levodopa 20 mg per mL)	Levodopa responsive, motor fluctuations	Nausea, vomiting, OH, GI procedure–related complications
Surgical treatment: GPi or STN DBS	Levodopa responsive, motor fluctuations, disabling dyskinesia, medication-refractory tremor	Does not help gait instability; contraindicated in moderate-severe cognitive impairment Cognitive and psychiatric symptoms may follow STN DBS

Abbreviations: COMT, catechol *O*-methyltransferase; DBS, deep brain stimulation; GI, gastrointestinal tract; GPi, globus pallidus pars interna; MAO, monoamine oxidase; OH, orthostatic hypotension; STN, subthalamic nucleus.

[a] Anticholinergics (eg, trihexyphenidyl) are used only rarely and are contraindicated in patients older than 65 years because of prominent autonomic and cognitive adverse effects.

[b] Immediate-release formulation: carbidopa 25 mg, levodopa 100 mg.

[c] Controlled-release formulation: carbidopa 50 mg, levodopa 200 mg.

[d] Extended-release formulation: Doses are shown as milligrams of carbidopa/milligrams of levodopa.

Long-term levodopa therapy leads to dyskinesias and motor fluctuations. Management strategies for motor fluctuations include the use of smaller and more frequent doses of levodopa, long-acting levodopa preparations (eg, carbidopa-levodopa extended-release formulations), dopamine agonists, and inhibitors of catechol *O*-methyltransferase. Apomorphine can be administered subcutaneously for severe akinesia at end-of-dose wearing-off times. Restricting protein to mealtimes may decrease unpredictable off times. Reducing the dose of levodopa can improve dyskinesia. Amantadine, a glutamate receptor antagonist, is used as adjuvant treatment in patients with levodopa-induced dyskinesias.

Carbidopa-levodopa enteral suspension, administered into the jejunum through a percutaneous endoscopic gastrostomy with jejunal tube, is an advanced therapy that can be used to treat medication-refractory motor fluctuations. Contraindications are concurrent use of nonselective monoamine oxidase inhibitors. Adverse effects are similar to those of other levodopa preparations in addition to the risk of gastrointestinal tract procedure–related complications.

Deep brain stimulation of the subthalamic nucleus or globus pallidus can relieve motor symptoms in eligible patients with levodopa-responsive Parkinson disease and medication-resistant tremor, severe motor fluctuations, or dyskinesia. Patient selection is critical to ensure maximal benefit from this therapy. Patients are not eligible if they have cognitive or psychiatric disorders or no response to levodopa. Manifestations such as dysphagia, postural instability, and gait freezing do not respond to the procedure. Deep brain stimulation of the subthalamic nucleus may result in transient cognitive or psychiatric manifestations. Suicide has been reported in some patients.

The management of nonmotor manifestations of Parkinson disease is summarized in Table 59.4. Orthostatic hypotension, constipation, bladder dysfunction, and other autonomic manifestations develop in many patients with parkinsonism. In these patients, Parkinson disease should be distinguished from multiple system atrophy. Findings suggestive of multiple system atrophy include lack of a predictable response to levodopa, cerebellar or pyramidal signs, severe orthostatic hypotension and urinary incontinence, and laryngeal stridor. The management of orthostatic hypotension includes eliminating potentially offending drugs (eg, vasodilators, diuretics, and dopamine agonists), increasing sodium and water intake, elevating the head of the bed, and wearing compression garments. Drug treatment includes fludrocortisone, midodrine, pyridostigmine, or the norepinephrine precursor dihydroxyphenylserine (droxidopa).

Table 59.4 • Management of Nonmotor Manifestations of Parkinson Disease

Manifestation	Mechanism	Management
Orthostatic hypotension	Loss of sympathetic ganglion neurons and effects of dopaminergic agonists	Increase sodium and water intake Fludrocortisone, midodrine, pyridostigmine, droxidopa
Constipation	Loss of enteric neurons	Bulk agents, enema
Insomnia	Wearing off; PLMS	Nightly dose of levodopa
REM sleep behavior disorder	Early manifestation	Clonazepam, melatonin
Hallucinations	Medication effect (exclude DLB)	Discontinue use of anticholinergics, MAO-B inhibitors, and amantadine Reduce or discontinue use of dopamine agonists Quetiapine, clozapine, pimavanserin
Depression	Loss of serotonergic neurons?	SSRIs Optimize dopaminergic therapy
Anxiety	Akathisia, stressors	Optimize dopaminergic therapy
Cognitive impairment	Frontal lobe dysfunction Development of DLB	Cholinesterase inhibitors Optimize dopaminergic therapy
Impulse dyscontrol (compulsive gambling, compulsive shopping, pathologic hypersexuality)	Activation of dopamine D_3 receptors in limbic striatum	Warn the patients Reduce or discontinue use of dopaminergic agonist Quetiapine or SSRI may help
Fatigue	Multifactorial	Optimize dopaminergic therapy
Pain	Early morning dystonia Immobility	Increase levodopa Mobilization, physical therapy
Arm paresthesia	May reflect insufficient levodopa treatment	Increase levodopa Exclude other causes
Diplopia	Medication effect Poor convergence	Reading glasses or prisms instead of bifocals

Abbreviations: DLB, dementia with Lewy bodies; MAO, monoamine oxidase; PLMS, periodic limb movements of sleep; REM, rapid eye movement; SSRI, selective serotonin reuptake inhibitor.

New-generation antipsychotic drugs, such as quetiapine or clozapine, are preferably used to manage drug-induced psychosis or hallucinations because they are less likely to exacerbate parkinsonism. Pimavanserin, a serotonin-selective inverse agonist, is a new antipsychotic drug that also will not exacerbate parkinsonism. It prolongs the QT interval, so it should be avoided in patients with known QT prolongation or cardiac arrhythmia and in patients receiving other drugs known to prolong the QT interval. It is metabolized by cytochrome P450 3A4 isozyme (CYP3A4). The most common adverse reactions are peripheral edema, nausea, confusional state, hallucinations, constipation, and gait disturbance. Typical neuroleptics (eg, haloperidol) and other dopaminergic-blocking medications (eg, metoclopramide) should be avoided in patients with parkinsonism or suspected Lewy body dementia.

KEY FACTS

- ✓ The first principle to consider for every patient with any type of movement disorder—potential adverse effect of medication
- ✓ Wilson disease—should be considered in young patients (<50 years old) with any type of movement disorder
- ✓ First-line treatment of essential tremor—β-blockers or primidone
- ✓ Manifestations that suggest an atypical parkinsonian syndrome—poor response to levodopa, early postural instability with falls, severe orthostatic hypotension, and early dementia
- ✓ Neuroleptics and other dopaminergic-blocking medications should be avoided in patients with parkinsonism or suspected Lewy body dementia

Dystonia

Dystonia is a movement disorder with sustained muscle contractions that produce involuntary twisting and repetitive movements and abnormal postures (choreoathetosis). There is inappropriate co-contraction of agonist and antagonist muscles. Dystonia is classified by etiology, distribution, or age at onset. Etiology can be primary (hereditary or idiopathic) or secondary. Distribution can be focal (1 limb or body part), segmental, multifocal, hemidystonia, or generalized. In children, it typically starts in a lower limb and becomes generalized and is often hereditary. In adults, it is typically focal at onset in the upper limb or head (eg, cervical dystonia, writer's cramp, and orofacial dystonia), with limited spread. Dystonia is usually induced by action and is absent at rest; it may be task-specific (eg, writer's cramp and musician's dystonia). There is often a sensory trick (eg, touching the affected body part) to suppress dystonia.

Key Definition

Dystonia: *a movement disorder with sustained muscle contractions that produce involuntary twisting and repetitive movements and abnormal postures (choreoathetosis).*

Young patients with focal, segmental, and generalized dystonia should undergo a trial with carbidopa-levodopa because some forms may be very sensitive to dopaminergic medication. Other medications for focal or generalized dystonia include anticholinergics, baclofen, and clonazepam. For severe medication-refractory dystonia, deep brain stimulation of the globus pallidus pars interna bilaterally is used; benefit can take weeks to months.

The first-line treatment of focal dystonia is botulinum toxin, which blocks the neuromuscular junction. This therapy is effective for cervical dystonia, blepharospasm, hemifacial spasm, spasmodic dysphonia, oromandibular dystonia, and limb dystonia, including occupational dystonias.

Acute dystonic reactions, including oculogyric crises, may be triggered (particularly in young patients) by drugs that block dopamine receptors, including antiemetics such as metoclopramide and antipsychotic agents (especially first-generation drugs such as haloperidol). In older patients, these drugs may typically trigger parkinsonism. Long-term use of dopaminergic agonists may result in *tardive dyskinesia*, characterized by stereotyped movements affecting the face, mouth, or other body parts. The usual treatment is to withdraw the offending medication. Valbenazine, a new medication approved for treatment of tardive dyskinesia, reversibly inhibits the vesicular monoamine transporter 2 (VMAT2), affecting the uptake of monoamines to the synaptic vesicle from the cytoplasm.

Chorea, Athetosis, and Ballismus

Chorea is characterized by rapid, random, flowing movements that affect the face, neck, or limbs. Patients may appear restless and can maintain postures only briefly (motor impersistence); for example, they may not be able to keep the tongue protruded or sustain a handgrip. Chorea has many causes, including vascular, postinfectious, autoimmune (including antiphospholipid antibody syndrome and checkpoint inhibitor medications), toxic-metabolic (thyrotoxicosis), and paraneoplastic conditions; pregnancy; and drugs (such as psychostimulants). Chorea is the typical motor manifestation of Huntington disease, in which it is associated with dementia and behavioral abnormalities. Antichorea medications include dopamine-depleting agents (eg, tetrabenazine), amantadine, and dopaminergic-blocking agents (typical and atypical antipsychotics, such as haloperidol and quetiapine).

Athetosis is a slow, writhing involuntary movement of the distal aspect of a limb caused by chorea superimposed on dystonia. *Choreoathetosis* describes the condition when chorea is more prominent; this most commonly occurs in cerebral palsy.

Ballismus is a severe form of chorea, with large-amplitude flailing movements, especially in the proximal aspects of limbs. It typically affects only 1 side of the body (*hemiballismus*) and is commonly due to a lesion of the contralateral subthalamic nucleus.

Myoclonus

Myoclonus is defined as sudden, lightning-like jerks of an entire muscle that moves a joint. In comparison, fasciculations or myokymia occurs in a segment of muscle and does not cause movement across the joint. These are simple movements and can be observed at rest or accentuated with posture or action. They can be low or high amplitude. They are not rhythmic like tremor and are briefer than tics. *Asterixis* is the opposite of myoclonus (negative myoclonus) and is due to loss of muscle tone. Myoclonus occurs in many toxic-metabolic disorders and some neurodegenerative disorders. Important examples are hypoxic-ischemic encephalopathy, medication effect (eg, opiates, tramadol, and antidepressants), renal or hepatic failure, mitochondrial disorders, and Creutzfeldt-Jakob disease.

Key Definition

Myoclonus: *sudden, lightning-like jerks of an entire muscle that moves a joint.*

Tics

Tics are sudden, rapid, involuntary movements (*motor tics*) or vocalizations (*vocal tics*) of varying intensity, frequency, and duration. They can be simple (eg, eye blink, head turn, cough, or sniff) or complex (eg, kicking, jumping, or vocalizing words). They wax and wane and are exacerbated with stress, anxiety, fatigue, and excitement. They can be decreased with concentration and are absent during sleep. A premonitory sensation (urge or tension) often occurs before the tics. They can be briefly suppressed, but suppression leads to increased tension followed by relief after the tics occur. Tics begin in childhood or adolescence and improve in the late teenaged years and early adulthood. Causes include genetic risk such as family history of tics or Tourette syndrome, autoimmune disorders, medications, and brain lesions.

Patients with Tourette syndrome have tics that occur before age 21 years, with multiple motor tics and at least 1 vocal tic for at least 12 months. Associated psychiatric comorbidities are obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, anxiety, or depression.

Treatment includes education, behavioral therapy for tic suppression, and medications. The medications are α_2-adrenergic agonists (eg, clonidine and guanfacine), dopamine blockers (eg, fluphenazine, risperidone, aripiprazole, quetiapine, haloperidol, and pimozide), dopamine-depleting agents (eg, tetrabenazine), dopamine agonists (eg, pramipexole), baclofen, topiramate, levetiracetam, clonazepam, and botulinum toxin (for simple motor tics). Deep brain stimulation can be used for severe tics refractory to medication.

Ataxia

Ataxia is a disorder of the cerebellum or its connections. Symptoms include unsteady gait, slurred speech, clumsy limbs, and diplopia. The signs include ataxic gait, dysarthria, finger-nose and heel-shin ataxia and dysmetria, intention tremor, nystagmus, impaired saccades, and rebound. Ataxia may be hereditary, acquired, or sporadic. For many patients, the cause can be determined on the basis of the age at onset, speed of progression (sudden, acute, subacute, or chronic), and presence of family history. There are many causes of ataxia. Some reflect focal cerebellar lesions, including vascular (eg, cerebellar stroke), infectious (eg, varicella, Lyme disease, or Whipple disease), demyelinating (eg, multiple sclerosis), and neoplastic (eg, cerebellar metastasis) lesions. Autoimmune causes include paraneoplastic disorders (eg, those associated with Purkinje cell antibodies in gynecologic malignancies) and nonparaneoplastic disorders (eg, celiac disease). Ataxia is also an important manifestation of toxic disorders (eg, involving alcohol, antiepileptic drugs, toluene, heavy metals, or chemotherapy) and metabolic disorders (eg, thiamine deficiency, hypothyroidism, vitamin E deficiency) and may be the presenting manifestation of prion disorders (eg, Creutzfeldt-Jakob disease). Genetic forms of ataxia include autosomal recessive, autosomal dominant, X-linked, and mitochondrial disorders. The presence of comorbidities (eg, diabetes mellitus, cataracts, or cardiomyopathy) or other neurologic signs (eg, ophthalmoplegia, peripheral neuropathy, or pyramidal signs) can help with the diagnosis. For patients with a positive family history of ataxia, genetic testing can be performed for autosomal dominant spinocerebellar ataxias, and autosomal recessive ataxias, such as Friedreich ataxia. To reduce morbidity, potentially treatable causes of hereditary ataxia must be identified with appropriate laboratory testing. In the absence of a reversible cause, treatment is mainly supportive with physical, occupational, and speech therapy.

Restless Legs Syndrome and Periodic Limb Movements of Sleep

Restless legs syndrome is a common movement disorder characterized by an unpleasant sensation (crawling, paresthesia) in the lower limbs (occasionally upper limbs) that typically emerges when sitting or lying down in the evening. It is relieved by limb movement or ambulation and is worsened by holding the limbs still. It occurs during wakefulness. Risk factors are family history, anemia, pregnancy, drugs, and alcohol. It improves with correction of anemia (ferritin value >50 mcg/L), hydration, exercise, and avoidance of alcohol. First-line treatment is gabapentin (or pregabalin) or a dopamine agonist (ropinirole, pramipexole). Patients receiving dopamine agonists should be counseled about the risk of impulse control disorders. Second-line agents are opioids or benzodiazepines.

Periodic leg movements of sleep are repetitive rhythmic leg flexion movements that occur only during sleep, and they sometimes lead to arousals from sleep. They differ from restless legs syndrome in that they are painless and the patient is asleep at onset and has no awareness of them. They frequently occur with restless legs syndrome, however. Typically, a spouse reports these movements, which wake the spouse from sleep. The movements are confirmed by history and polysomnography. Treatment includes dopamine agonists and gabapentin.

KEY FACTS

- ✓ Acute onset of unilateral dystonia, chorea, or ballismus—suggests a vascular lesion in the contralateral cerebral hemisphere
- ✓ Subacute onset of generalized chorea or other movement disorder—suggests an immune cause, including paraneoplastic syndrome
- ✓ Treatment of focal dystonia—botulinum toxin
- ✓ Primary treatment of restless legs syndrome and periodic limb movements of sleep—dopamine agonist or gabapentin (or pregabalin)
- ✓ Patients receiving dopamine agonist therapy for Parkinson disease, restless legs syndrome, or periodic limb movements of sleep should be made aware of the risk of impulse control disorders, including compulsive gambling, pathologic hypersexuality, or compulsive shopping

60

Neoplastic Diseases

ALYX B. PORTER, MD

Primary Neoplasms of the Central Nervous System

Brain tumors may manifest with focal progressive neurologic deficits, increased intracranial pressure (causing headache, vomiting, and papilledema), new-onset seizures, or progressive cognitive and behavioral changes. The most common primary brain tumors in adults are meningioma, astrocytoma, oligodendroglioma, and lymphoma. Contrast-enhanced magnetic resonance imaging (MRI) is the gold standard for imaging of the central nervous system (CNS) when malignancy is suspected. Contrast-enhanced computed tomography (CT) may be considered if MRI is contraindicated.

The main risk factors associated with meningioma are syndromes associated with genetic predisposition and ionizing radiation (Figure 60.1). Treatment options vary according to patient age, comorbid conditions, tumor size, location, progression, and histologic characteristics. Small asymptomatic tumors should be observed with follow-up CT or MRI every 6 to 12 months. If symptoms develop or if tumor growth has clearly occurred, surgical resection is indicated. Postoperative radiotherapy is indicated for incomplete resection, for tumors with aggressive histologic features (anaplastic or malignant meningiomas), or for disease recurrence. Stereotactic radiosurgery is a treatment option for some patients. Chemotherapeutic options are limited.

Of all primary CNS neoplasms, 40% are gliomas, which are infiltrative tumors that occur in all areas of the brain and spinal cord. They are classified as grades 1 through 4 according to their histologic features. Patients with gliomas may present with various symptoms that reflect the tumor location. The prognosis depends on the patient's age at diagnosis, the patient's performance status, the resectability of the tumor, and the tumor type. Among patients with low-grade astrocytoma, median survival is 6 to 8 years; among patients with low-grade oligodendroglioma, about 10 years. Clinical and radiologic observation is a reasonable approach for patients with stable lesions that appear to be low grade and are in a nonresectable area of the brain. Patients with large lesions, contrast enhancement or possible hemorrhage, and mass effect are candidates for surgical resection. The role of postoperative radiotherapy and chemotherapy is controversial for patients with low-grade glioma.

High-grade astrocytomas, including anaplastic (grade 3) astrocytoma, anaplastic oligodendroglioma (grade 3 oligodendroglioma), and glioblastoma multiforme (grade 4), are generally associated with poor prognosis and limited survival (about 17.7% at 1 year) (Figure 60.2). Surgical therapy is important for obtaining a tissue diagnosis (which is heavily dependent on molecular features), reducing the mass effect, and removing the majority of the lesion. After surgical therapy, radiotherapy is administered at the site of the lesion. Patients who receive concurrent temozolomide and radiotherapy and subsequent adjuvant temozolomide have longer survival than those who receive radiotherapy alone. Tumor-treating fields are a novel therapy that help improve overall survival when added to chemoradiotherapy for patients with newly diagnosed glioblastoma.

Primary central nervous system lymphoma is typically a diffuse large B-cell lymphoma that is confined to the brain and the spinal cord and is becoming more common in both immunosuppressed and immunocompetent patients. Imaging features are typically consistent with homogeneously enhancing lesions that may be multifocal (Figure 60.3). These lesions may also appear to be necrotic or ring-enhancing, particularly in patients who are immunosuppressed. Diagnosis is made by cytologic analysis of cerebrospinal fluid or brain biopsy. Surgical resection is indicated only for reduction of considerable mass effect. Treatment emphasizes chemotherapy and stem-cell transplant; radiotherapy is used mainly for disease recurrence and palliation. With improved treatment techniques, median survival has increased to approximately 2 years or more.

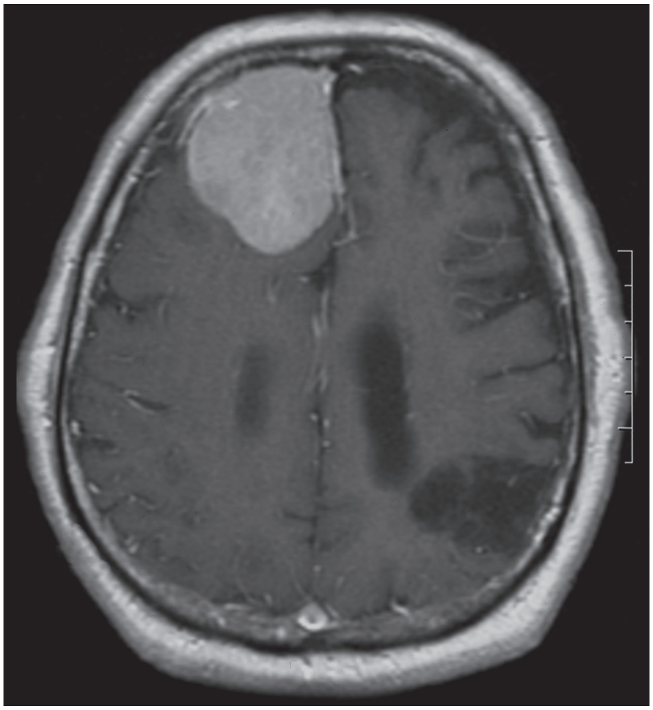

Figure 60.1. *Magnetic Resonance Imaging of a Large Right Frontal Meningioma. Characteristic dural tail and nearly homogeneous enhancement (gadolinium-enhanced axial T1-weighted sequence) are present.*

(From Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627-778; used with permission of Mayo Foundation for Medical Education and Research.)

Key Definition

Primary central nervous system lymphoma: *a diffuse large B-cell lymphoma that is confined to the brain and the spinal cord.*

Neurologic Manifestations in Patients With Systemic Cancer

The most common neurologic symptoms of patients with systemic cancer are back pain, altered mental status, and headache. However, the most common neurologic complication of systemic cancer is metastatic disease, of which cerebral metastasis is the most frequent. In patients with cancer and back pain, epidural metastasis and direct vertebral metastasis are common, but 15% to 20% of patients do not have a malignant diagnosis. Nonstructural causes are the most common reasons for headache in this patient population. Identified causes include fever, adverse effects of therapy, metastasis (cerebral, leptomeningeal, or base of skull), and intracranial hemorrhage (thrombocytopenia or hemorrhage due to intracranial metastasis). The most common cause of altered mental status is toxic-metabolic encephalopathy, which is also the most common nonmetastatic manifestation of systemic cancer. The diagnosis of encephalopathy is made when patients have altered mental status with no structural cause identified on imaging and no other explanation from electroencephalography. Less common causes of altered mental status in these patients include intracranial metastatic disease (parenchymal and meningeal), paraneoplastic limbic encephalitis, intracranial hemorrhage, primary dementia, cerebral infarction, psychiatric disorder, known primary brain tumor, bacterial meningitis, and transient global amnesia.

Many neurologic problems in patients with cancer can be diagnosed from the medical history and findings on neurologic examination and require knowledge of neurologic illness unrelated to metastasis or cancer.

Neurologic complications of systemic cancer are listed in Box 60.1.

KEY FACTS

- ✓ Brain tumors—may manifest with focal progressive neurologic deficits, increased intracranial pressure (causing headache, vomiting, and papilledema), new-onset seizures, or progressive cognitive and behavioral changes
- ✓ Most common primary brain tumors in adults—meningioma, astrocytoma, oligodendroglioma, and lymphoma
- ✓ Treatment of primary central nervous system lymphoma emphasizes chemotherapy and stem-cell transplant; radiotherapy is used mainly for disease recurrence and palliation

Metastasis to the Brain

Brain metastases are the most common brain tumors (Figure 60.4). Approximately 30% of cancer patients have brain metastasis at presentation or later. Metastatic lung cancer is the most common primary cancer that metastasizes to the brain (40%-50% of patients); other common types are breast cancer, colon cancer, melanoma, and unknown primary cancer. Melanoma produces a disproportionate number of metastases in the CNS. Evaluation includes detailed history and examination, assessment of medical and neurologic

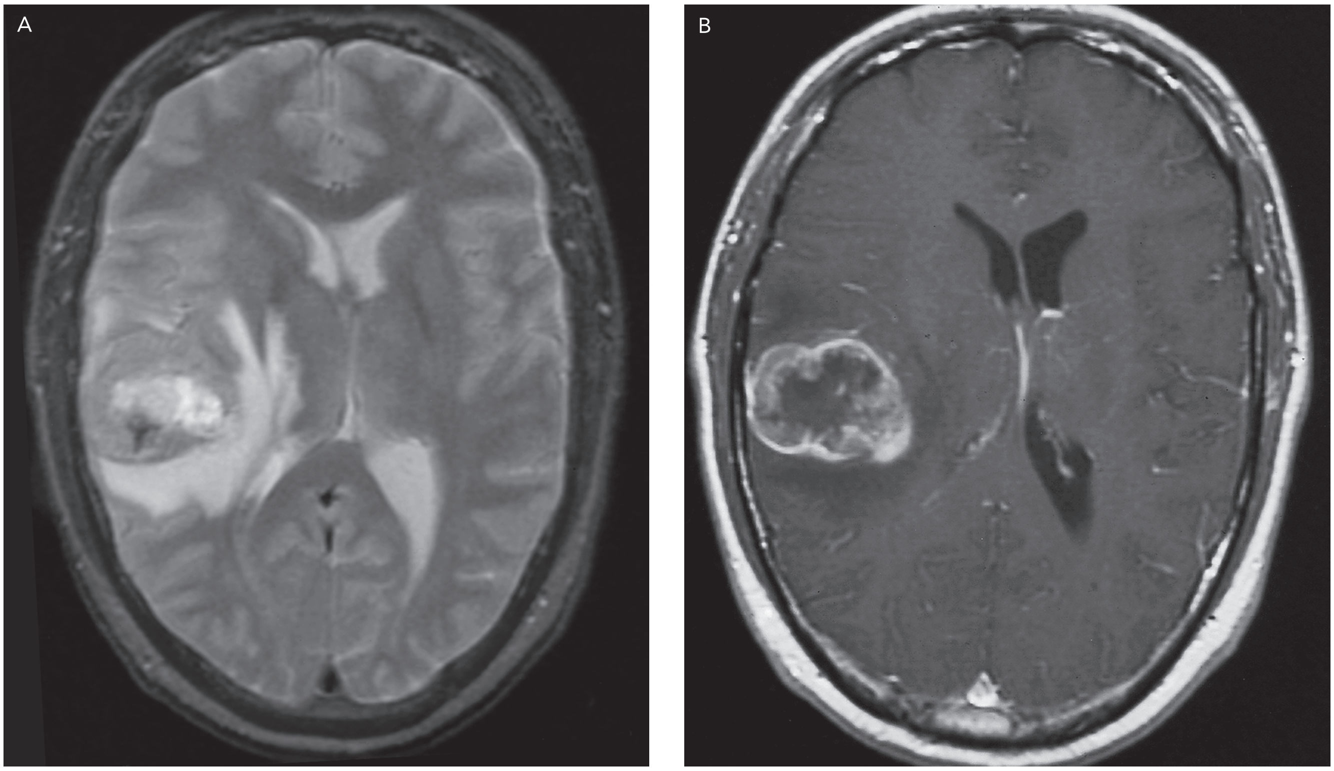

Figure 60.2. *Magnetic Resonance Imaging From a 33-Year-Old Patient With Glioblastoma Multiforme. T2-weighted imaging (A) and contrast-enhanced T1-weighted imaging (B) show a peripherally enhancing mass with a heterogeneous signal within the lesion, situated in the junction of the right posterior frontotemporal operculum and insula. Vasogenic edema is present in the white matter surrounding the lesion and is associated with mass effect and a right-to-left midline shift.*

(From Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627-778; used with permission of Mayo Foundation for Medical Education and Research.)

performance status, and imaging studies (eg, MRI of the brain with gadolinium; CT of the chest, abdomen, and pelvis; and positron emission tomography). Brain metastases are frequently associated with surrounding edema, and dexamethasone is indicated (10 mg once and then 4 mg 2-4 times daily intravenously or orally), but additional treatment is required to prolong survival. Among untreated patients, median survival is 1 to 2 months; among treated patients, 2 to 10 months.

Survival depends on patient age, performance status, presence or absence of extracranial metastasis, and control of the primary tumor. Surgical resection of single accessible lesions increases survival among patients with good prognostic factors. Currently, most patients undergo stereotactic radiosurgery (SRS) for up to 10 lesions. Whole-brain radiotherapy is reserved for patients who have more than 10 lesions and for patients who need salvage therapy for progression after SRS. SRS can be used to treat multiple lesions in a single session and is associated with decreased risk of cognitive impairment.

Metastasis to the Spinal Cord, Leptomeninges, or Peripheral Nerves

Epidural spinal cord compression is the most common cause of spinal cord dysfunction in patients with cancer and is frequently preceded by vertebral metastasis. The most common causes are lung, breast, and prostate cancer; others are non-Hodgkin lymphoma, multiple myeloma, and colorectal or renal carcinoma. About 60% of all cases involve the thoracic spine, and multiple sites are involved in one-third of the patients. The cardinal symptom is back pain; other symptoms are weakness, sensory loss, and bladder or bowel dysfunction. Epidural spinal cord compression should be considered in all patients with any type of cancer and back or radicular pain. Contrast-enhanced MRI of the spine is the gold standard for diagnosis.

Dexamethasone is highly effective for ameliorating symptoms. In many patients, radiotherapy is efficacious for preventing

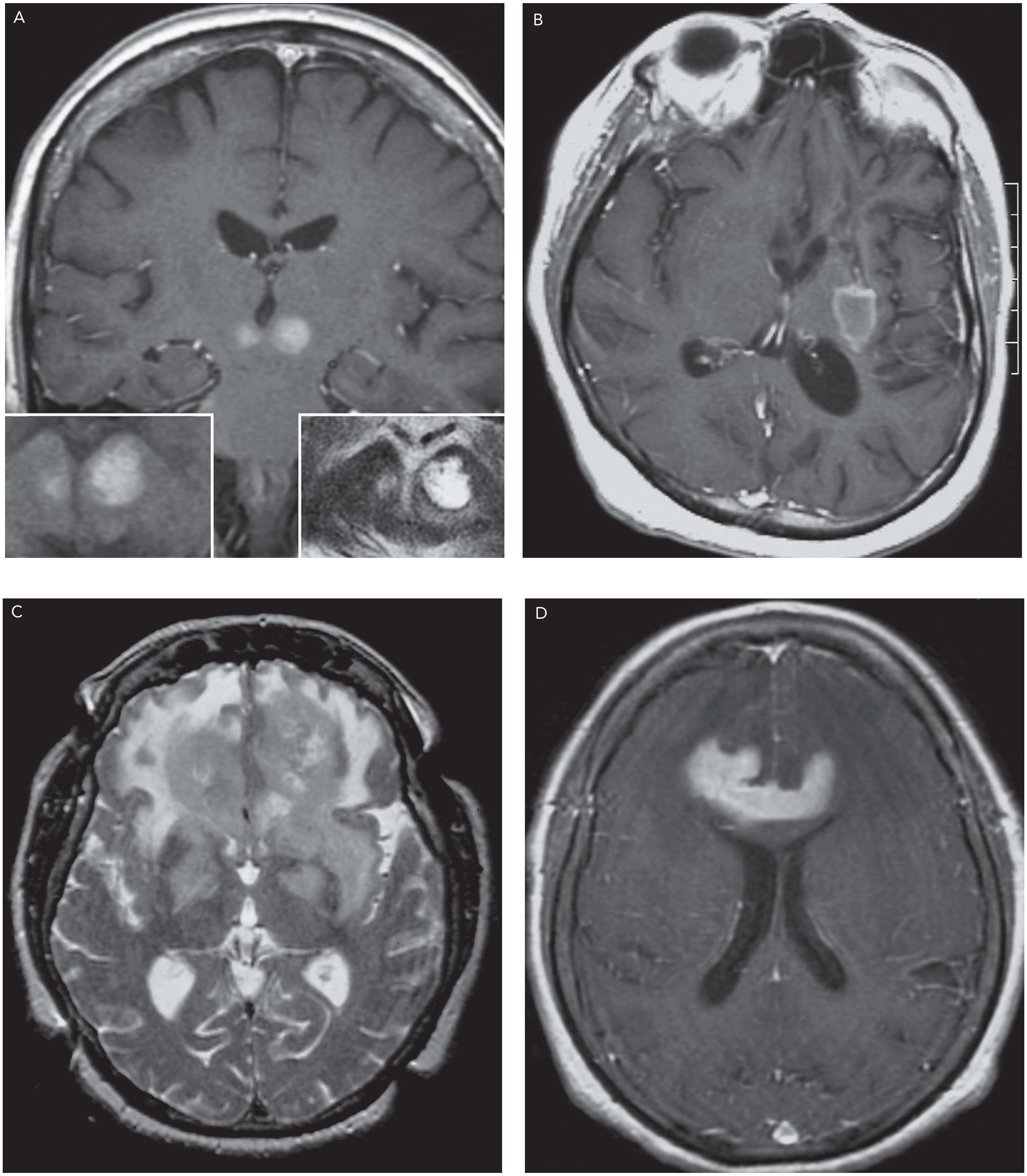

Figure 60.3. *Magnetic Resonance Imaging of Primary Central Nervous System Lymphoma. A, A 64-year-old woman with diffuse large B-cell lymphoma presented with worsening mental status. Gadolinium-enhanced T1-weighted image shows lesions in deep gray matter appearing as mirror images. Both pregadolinium T1-weighted image (left inset) and T2-weighted image (right inset) show increased signal, suggestive of subacute hemorrhage into the mass. B, Gadolinium-enhanced T1-weighted image from an 18-year-old woman with diffuse large B-cell lymphoma shows ring-enhancement outlining the lesion in deep gray matter (a common location for lymphoma). C and D, T2-weighted image (C) and gadolinium-enhanced T1-weighted image (D) from a different patient with diffuse large B-cell lymphoma show a large intraparenchymal mass in the frontal lobes bilaterally and extending through the genu of the corpus callosum and involving deep gray matter. Extensive perilesional vasogenic edema appears to be with mass effect on the frontal horns of the lateral ventricles.*

(From Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627-778; used with permission of Mayo Foundation for Medical Education and Research.)

Box 60.1 • Neurologic Complications of Systemic Cancer

Metastatic: parenchymal, leptomeningeal, epidural, subdural, brachial plexus, lumbosacral plexus, and nerve infiltration; these complications are common

Infectious: unusual central nervous system infections because of immunosuppression

Complications of systemic metastases: hepatic encephalopathy

Vascular complications: cerebral infarction from hypercoagulable states, nonbacterial thrombotic endocarditis, and radiation damage to carotid arteries; cerebral hemorrhage (eg, from thrombocytopenia and hemorrhagic metastases)

Toxic-metabolic encephalopathies: usually from multiple causes, hypercalcemia, syndrome of inappropriate secretion of antidiuretic hormone, medications, and systemic infections

Complications of treatment (radiotherapy, chemotherapy, or surgery): radiation necrosis of the brain, radiation myelopathy, radiation plexopathy, fibrosis of the carotid arteries, neuropathies, encephalopathies, and cerebellar ataxia

Paraneoplastic (ie, nonmetastatic or "remote" effect of cancer): rare syndromes have been described from the cerebral cortex through the central and peripheral neuraxes to muscle

Miscellaneous: various systemic and neurologic illnesses unrelated to cancer

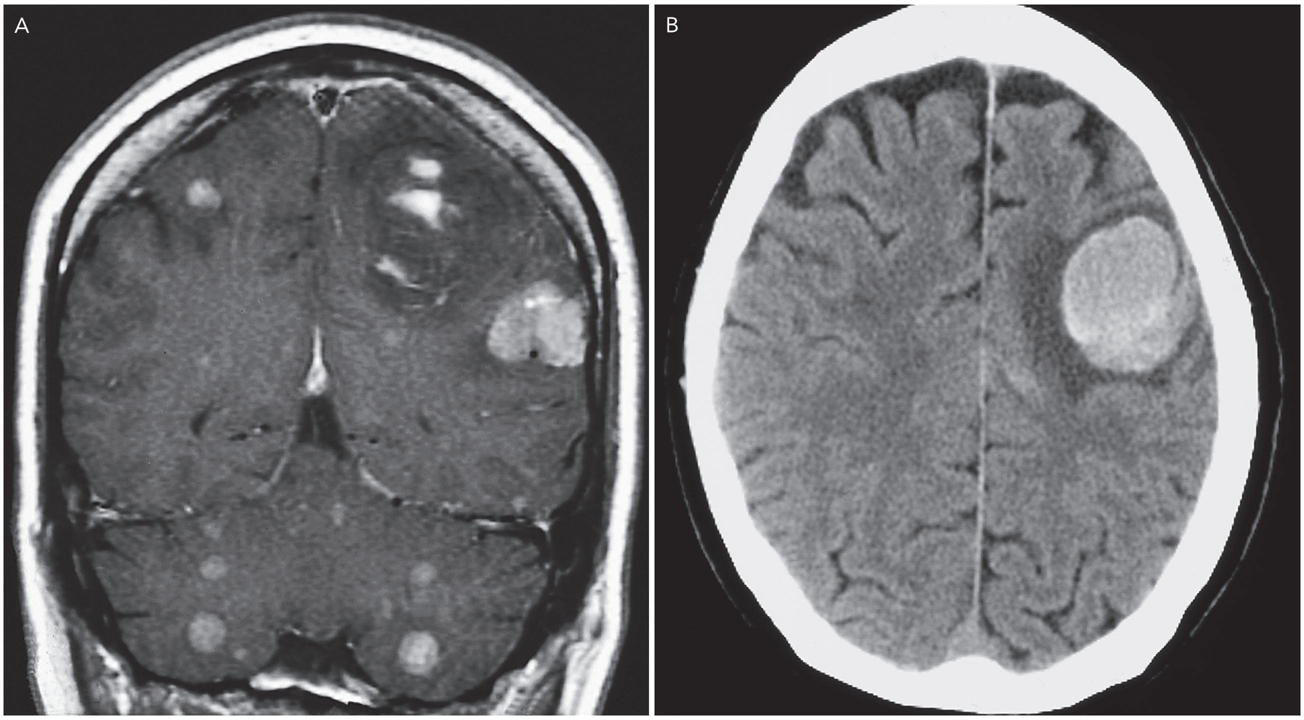

Figure 60.4. *Neuroimaging of Metastatic Cancer. Single or multiple enhancing lesions are seen at the junction of gray matter and white matter with various degrees of surrounding vasogenic edema, hemorrhage, or necrosis. A, Gadolinium-enhanced coronal T1-weighted image of metastatic melanoma shows numerous enhancing masses throughout the brain. B, Unenhanced computed tomogram from a different patient with metastatic melanoma shows subacute hemorrhage into the metastatic focus at the parasagittal posterior left frontal cortex. C and D, Axial fluid-attenuated inversion recovery image (C) and the enhanced axial T1-weighted image (D) show 2 enhancing foci of metastasis at the junction of gray matter and white matter, with surrounding vasogenic edema. The primary tumor was metastatic lung adenocarcinoma.*

(From Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627-778; used with permission of Mayo Foundation for Medical Education and Research.)

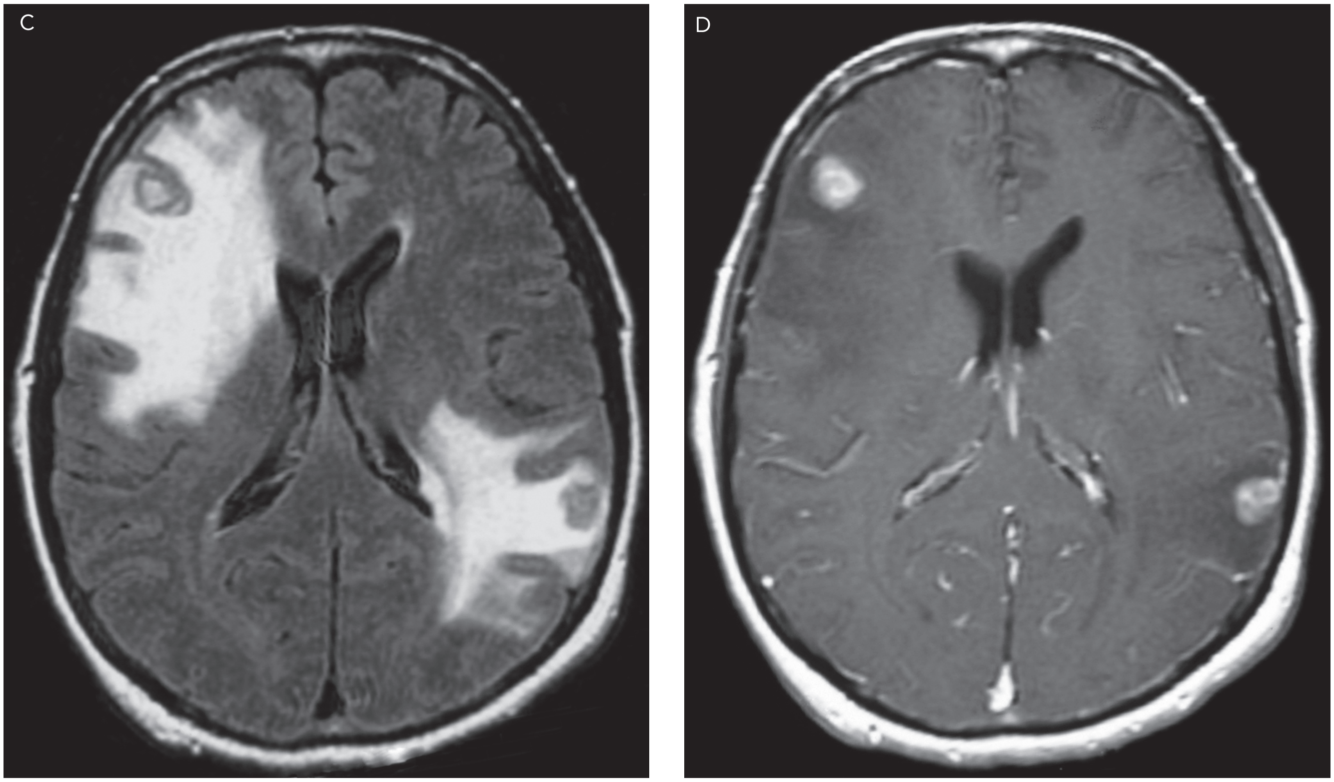

Figure 60.4. *Continued*

further tumor growth and neural damage. The therapeutic response is better with radiosensitive tumors (eg, multiple myeloma, lymphoma, and prostate, breast, and small cell lung carcinoma) than with relatively radioresistant tumors (eg, melanoma and renal cell carcinoma). Surgery is indicated for patients with spinal instability, bone impingement on the spinal cord, worsening deficits during or despite radiotherapy, radioresistant epidural tumors with limited tumor elsewhere, or a diagnosis that is in doubt.

Leptomeningeal metastases occur most frequently in lung and breast cancer, melanoma, leukemia, and lymphoma. Patients typically present with symptoms and signs reflecting involvement at many levels of the nervous system: headache, encephalopathy, seizures, cranial nerve involvement (most commonly diplopia or facial weakness), back pain, or spinal root involvement. Diagnosis is suggested by the presence of meningeal enhancement on MRI with gadolinium and is confirmed with cerebrospinal fluid cytologic findings. Subsequent cerebrospinal fluid samples may be necessary; the yield is 90% after the third lumbar puncture.

Intramedullary spinal cord metastases are much less frequent than epidural metastases and most commonly result from small cell lung carcinoma. Brachial plexus involvement is most frequent with lung and breast cancer as a result of direct tumor invasion. Colorectal cancer causes local pelvic metastasis and is the most frequent cause of neoplastic lumbosacral plexopathy. Head and neck cancers are the most frequent sources of metastasis to the base of the skull.

Paraneoplastic Disorders

Paraneoplastic disorders are associated with increased levels of circulating antibodies (*onconeural antibodies*) that are directed against neoplastic cells and attack membrane ion channels or intracellular (nuclear or cytoplasmic) proteins in neurons. The most common underlying malignancies are small cell lung carcinoma and breast cancer. Others include ovarian or testicular carcinoma, thymoma, Hodgkin disease, and parotid tumors. Paraneoplastic syndromes can affect any level of the CNS or peripheral nervous system (Box 60.2). Important examples include myasthenia gravis, limbic encephalitis (characterized by behavioral and memory abnormalities and seizures), brainstem encephalitis, opsoclonus-myoclonus, cerebellar ataxia, myelopathy, peripheral neuropathy, stiff-person syndrome (with axial and limb rigidity), sensory ganglionopathies, Lambert-Eaton myasthenic syndrome, dermatomyositis, and retinopathy. These syndromes are characterized by an acute or subacute

Box 60.2 • Classification of Paraneoplastic Neurologic Disorders

- Central nervous system
    - Encephalomyelitis
    - Limbic encephalitis
    - Cerebellar degeneration
    - Brainstem encephalitis
    - Opsoclonus-myoclonus
    - Stiff-person syndrome
    - Chorea
    - Necrotizing myelopathy
    - Motor neuronopathy
- Dorsal root ganglion and peripheral nerves
    - Subacute sensory neuronopathy
    - Gastroparesis or intestinal pseudo-obstruction
    - Acute autonomic ganglionopathy
    - Acquired neuromyotonia
    - Neuropathy associated with plasma cell dyscrasia or lymphoma
    - Vasculitis of nerve or muscle
    - Optic neuropathy
- Neuromuscular junction
    - Lambert-Eaton myasthenic syndrome
    - Myasthenia gravis
- Muscle
    - Dermatomyositis
    - Polymyositis
    - Acute necrotizing myopathy
- Eye and retina
    - Cancer-associated retinopathy

Table 60.1 • Paraneoplastic Antibodies Associated With Cancer and Syndromes

Antibody	Associated Cancer	Associated Syndromes
Anti-Hu (ANNA-1)	SCLC	Encephalomyelitis Limbic encephalitis Cerebellar degeneration SSN Autonomic ganglionopathy
Anti-Ri (ANNA-2)	Breast, gynecologic, SCLC	Ataxia Opsoclonus-myoclonus Brainstem encephalitis
Anti-Yo (PCA-1)	Breast, ovary	Cerebellar degeneration
CRMP-5	SCLC, thymoma	Chorea, myelopathy, optic neuritis, retinopathy, and others
Amphiphysin	Breast, SCLC	Stiff-person syndrome Encephalomyelitis
Anti-Ma2	Testicular germinoma	Limbic encephalitis Brainstem encephalitis
P/Q-type VGCC	SCLC	LEMS
Muscle nAChR	Thymoma	Myasthenia gravis
Ganglionic nAChR	SCLC	Autonomic ganglionopathy
Voltage-gated potassium channel	Thymoma, SCLC	Neuromyotonia Limbic encephalitis
NMDA receptor	Ovarian teratoma	Limbic encephalitis Rigidity Hypoventilation Dysautonomia

Abbreviations: ANNA, antineuronal nuclear antibody; CRMP, collapsin response mediator protein; LEMS, Lambert-Eaton myasthenic syndrome; nAChR, nicotinic acetylcholine receptor; NMDA, *N*-methyl-D-aspartate; PCA, Purkinje cell antibody; SCLC, small cell lung carcinoma; SSN, subacute sensory neuronopathy; VGCC, voltage-gated calcium channels.

onset and increased levels of 1 or more antibodies (Table 60.1). A paraneoplastic neurologic syndrome precedes the diagnosis of cancer in 60% of patients and develops after tumor diagnosis or at tumor recurrence in 40%.

Treatment of the underlying neoplasm is the main factor associated with neurologic stabilization. Immunotherapy with corticosteroids, intravenous immunoglobulin, plasma exchange, cyclophosphamide, or rituximab may be helpful in paraneoplastic disorders related to antibodies against membrane antigens such as P/Q-type voltage-gated calcium channels (Lambert-Eaton myasthenic syndrome) or voltage-gated potassium channels (limbic encephalitis) (Figure 60.5).

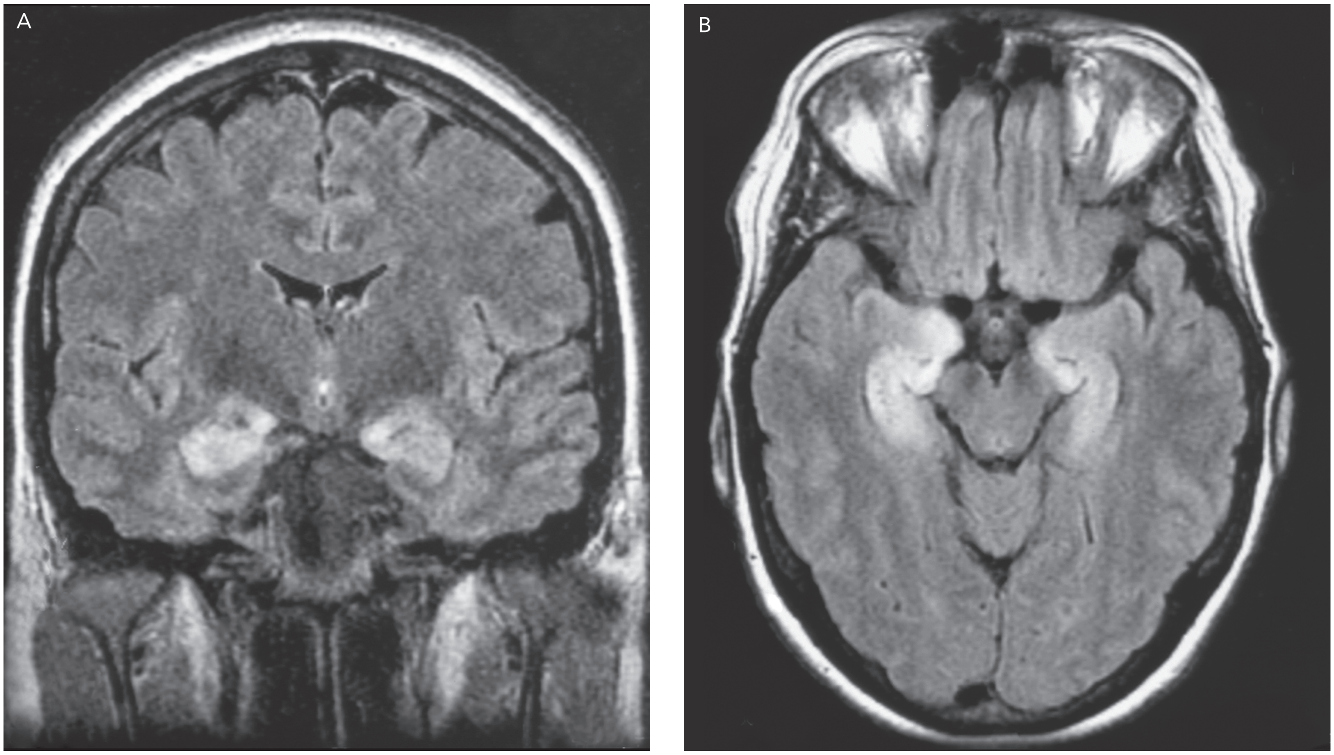

Figure 60.5 *Magnetic Resonance Imaging Characteristics of Paraneoplastic Limbic Encephalopathy in a Patient With Small Cell Lung Carcionoma. Coronal (A) and axial (B) fluid-attenuated inversion recovery sequences show increased signal within mesial temporal lobes bilaterally. The lesions were nonenhancing (not shown).*

(From Mowzoon N, Vernino S. Neoplasms of the nervous system and related topics. In: Mowzoon N, Flemming KD, editors. Neurology board review: an illustrated study guide. Rochester [MN]: Mayo Clinic Scientific Press and Florence [KY]: Informa Healthcare USA; c2007. p. 627-778; used with permission of Mayo Foundation for Medical Education and Research.)

Table 60.2 • Examples of Neurotoxicity of Chemotherapeutic Agents

Agent	Typical Manifestations of Neurotoxicity
Platinum compounds (cisplatin, oxaliplatin)	Sensory (large fiber) neuropathy (sensory ataxia) Autonomic neuropathy Ototoxicity Encephalopathy, cortical blindness, seizures Retrobulbar neuritis Retinal injury
Vinca alkaloids	Sensorimotor peripheral neuropathy Autonomic neuropathy
Taxanes (eg, paclitaxel)	Predominantly sensory peripheral neuropathy Occasional motor neuropathies Transient scotomata
Methotrexate	Acute chemical arachnoiditis (intrathecal administration) Acute, reversible, strokelike syndrome Subacute encephalopathy Transverse myelopathy Chronic demyelinating encephalopathy

Table 60.2 • Continued

Agent	Typical Manifestations of Neurotoxicity
5-Fluorouracil	Cerebellar dysfunction Acute encephalopathy Subacute extrapyramidal syndrome Leukoencephalopathy (when combined with levamisole)
Cytarabine (ara-C)	Cerebellar dysfunction Cognitive impairment Necrotizing leukoencephalopathy Peripheral neuropathy Seizures, parkinsonism, myelopathy
Ifosfamide	Encephalopathy with agitation, visual and auditory hallucinations, behavioral and memory changes Hemiparesis, seizures, coma Cerebellar, extrapyramidal, or cranial nerve dysfunction
Nitrosoureas	Encephalopathy
Busulfan	Seizures
L-Asparaginase	Encephalopathy Cerebral venous thrombosis

KEY FACTS

- ✓ Brain metastases—most common brain tumors
- ✓ Cancer metastatic to the brain—most common is lung cancer (40%-50% of patients); others are breast cancer, colon cancer, melanoma, and unknown primary cancer
- ✓ Epidural spinal cord compression—the most common cause of spinal cord dysfunction in patients with cancer; frequently preceded by vertebral metastasis
- ✓ Cardinal symptom of epidural spinal cord compression—back pain; other symptoms are weakness, sensory loss, and bladder or bowel dysfunction
- ✓ Paraneoplastic diseases—most common underlying malignancies are small cell lung carcinoma and breast cancer

Neurologic Complications of Cancer Treatment

Treatment of cancer with chemotherapeutic and biologic agents is frequently complicated by the development of neurotoxicity. Typical examples are listed in Table 60.2.

61 Seizure Disorders

LILY C. WONG-KISIEL, MD

***Seizures* are electroclinical** events, and *epilepsy* indicates a tendency for recurrent unprovoked seizures. The updated classification for seizures is given in Table 61.1.

The proper treatment of epilepsy depends on accurate diagnosis of the seizure type, identification of the cause (if possible), and management of psychosocial problems. Electroencephalography (EEG) (preferably after the patient is sleep deprived) can be important for classifying the type of seizure. Magnetic resonance imaging is also used to evaluate for focal or structural lesions. Much of the diagnosis rests on a supportive history. An aura and a period of altered mental status after the spell (*postictal confusion*) are highly suggestive of an epileptic seizure.

Causes

Seizures occur at any age, but approximately 70% of all patients with epilepsy have their first seizure before age 20 years. Age distribution for the onset of epilepsy is bimodal, with the second most common group being the elderly population. Both the cause and the type of epilepsy are related to age at onset. However, the cause may not be found in many patients.

Neonatal seizures are often due to congenital defects or prenatal injury, and head trauma is often the cause of focal seizures in young adults. Brain tumors and vascular disease are major known causes of seizures in later life. Seizures often occur during withdrawal from alcohol, barbiturates, or benzodiazepines in young and old adults. Seizures also occur with the use of drugs such as cocaine, usually in young adults. Metabolic derangements (eg, hypoglycemia, hypocalcemia, hyponatremia, and hypernatremia) can occur at any age, as can infections (eg, meningitis and encephalitis). Metabolic abnormalities usually cause primary generalized tonic-clonic seizures and rarely focal or multifocal seizures. Central nervous system infections usually cause partial and secondary generalized tonic-clonic seizures.

In contrast to epileptic seizures, **psychogenic nonepileptic events or episodes** (ie, pseudoseizures or psychogenic nonepileptic seizures) are sudden changes in behavior or mentation not associated with any physiologic cause or abnormal paroxysmal discharge of electrical activity from the brain. Events are frequent and resistant to antiepileptic treatment, affecting about 30% of patients referred for medically refractory epilepsy. The diagnosis of psychogenic nonepileptic events is supported by simultaneous video and EEG documentation of typical symptoms with no abnormal EEG before, during, or after the symptoms of concern. A favorable outcome may be associated with an independent lifestyle, the absence of coexisting epilepsy, and a formal psychologic approach to therapy. There is growing evidence for the efficacy of cognitive behavior therapy.

Key Definition

Psychogenic nonepileptic events or episodes (ie, pseudoseizures or psychogenic nonepileptic seizures): *sudden changes in behavior or mentation not associated with any physiologic cause or abnormal paroxysmal discharge of electrical activity from the brain.*

Clinical and Laboratory Diagnostic Evaluation

Magnetic resonance imaging is used to investigate the underlying structural abnormality, and EEG is important for

Table 61.1 • Seizure Types and Terminology Used in 1981 and 2017

Mode of Onset	1981	2017
Focal	Simple partial seizures Simple partial sensory Simple partial motor Simple partial special sensory (unusual smells or tastes)	Focal aware Motor onset (automatisms, atonic, clonic, epileptic spasms, hyperkinetic, myoclonic, tonic)
	Speech arrest or unusual vocalization	Nonmotor onset (autonomic, behavior arrest, cognitive, emotional sensory)
	Complex partial seizures Consciousness impaired at onset Simple partial onset followed by impaired consciousness	Focal impaired awareness Motor onset (automatisms, atonic, clonic, epileptic spasms, hyperkinetic, myoclonic, tonic) Nonmotor onset (autonomic, behavior arrest, cognitive, emotional sensory)
	Evolving to generalized tonic-clonic convulsions (secondary generalized tonic-clonic seizures) Simple evolving to generalized tonic-clonic	Focal to bilateral tonic-clonic
	Complex evolving to generalized tonic-clonic (including those with simple partial onset)	
Generalized	Tonic-clonic Myoclonic	Generalized onset Motor onset (tonic-clonic, clonic, tonic, myoclonic, myoclonic-tonic-clonic, myoclonic-atonic, atonic, epileptic spasms)
	Absence and atypical absence	Nonmotor onset (absence) Typical, atypical, myoclonic, eyelid myoclonia
	Clonic Tonic Atonic	
Not clear	Unclassified	Unknown onset
		Motor onset Nonmotor onset
		Unclassified

Data from Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr;58(4):522-30.

deciding whether to treat a first unprovoked seizure. The risk of recurrent seizures is high if the initial EEG shows epileptiform activity; the risk is low if the EEG findings are normal. Laboratory tests for inherited neurometabolic, developmental, and degenerative disorders can be considered for children and for patients with a progressive course. For patients with febrile illness, lumbar puncture should be considered to assess the cerebrospinal fluid for central nervous system infection.

KEY FACTS

- ✓ EEG (preferably after the patient is sleep deprived)—important for the classification of seizure type
- ✓ Magnetic resonance imaging—used to evaluate for focal or structural lesions
- ✓ Diagnosis of epilepsy—much of the diagnosis rests on a supportive history
- ✓ Features highly suggestive of an epileptic seizure—an aura and a period of altered mental status after the spell (postictal confusion)

Anticonvulsant Therapy

Drugs used to treat seizures are listed in Table 61.2. Monotherapy is the treatment of choice. The dosage may be increased as high as necessary and to as much as can be tolerated. The coadministration of antiepileptic drugs has not been shown to have more antiseizure efficacy than the administration of only 1 drug without concurrently increasing toxicity. In studies of a large population, a particular drug may be shown to be more efficacious and less toxic, but for a given patient, another drug may be more effective or have fewer adverse effects. Older antiepileptic drugs include phenytoin, carbamazepine, valproic acid, benzodiazepines, and ethosuximide. The newer antiepileptic drugs include gabapentin, tiagabine, lamotrigine, topiramate, felbamate, zonisamide, oxcarbazepine, levetiracetam, pregabalin, lacosamide, rufinamide, vigabatrin, clobazam, perampanel, and brivaracetam. These agents generally have less potential for drug interactions and fewer adverse effects than the older drugs.

Choice of antiepileptic drug depends on seizure type or epilepsy syndrome. Some antiepileptic drugs have a narrow spectrum and are effective for a specific seizure type or epilepsy syndrome (eg, ethosuximide for childhood absence epilepsy). Other antiepileptic drugs may in fact exacerbate certain seizure types: carbamazepine, gabapentin, oxcarbazepine, pregabalin, and tiagabine may aggravate myoclonic and absence seizures. When seizures cannot be classified as focal or generalized, a

Table 61.2 • Guidance for Use of Antiepileptic Drugs

Criteria	Possibilities	Drug
Type of seizures	Focal seizures with or without secondary GTCSs	PHT, CBZ, oxcarbazepine, pregabalin, tiagabine, lacosamide, perampanel
	Focal and generalized seizures	VPA, PB, benzodiazepines, lamotrigine, levetiracetam, topiramate, zonisamide, felbamate, brivaracetam
	Absence seizures	Ethosuximide, VPA, lamotrigine
	Myoclonic seizures	VPA, clonazepam, lamotrigine, zonisamide, levetiracetam, brivaracetam
	Atonic, akinetic, or mixed seizures	VPA, felbamate, topiramate, lamotrigine, rufinamide
Use of other drugs metabolized in the liver	Drugs that do not affect metabolism of other drugs	Gabapentin, pregabalin, tiagabine, lamotrigine, zonisamide, levetiracetam, rufinamide, lacosamide, brivaracetam
Avoidance of oral contraceptive pill failure	Drugs with no or minimal effect on contraceptive metabolism	VPA, clonazepam, gabapentin, pregabalin, tiagabine, lamotrigine, zonisamide, levetiracetam, lacosamide

Abbreviations: CBZ, carbamazepine; GTCS, generalized tonic-clonic seizure; PB, phenobarbital; PHT, phenytoin; VPA, valproic acid.

broad-spectrum antiepileptic drug for both focal and generalized epilepsy is preferred. Because the efficacy, cost, and dosing schedule (twice daily) are similar for many of the new anticonvulsants, tolerability is frequently the major determinant in choosing a particular drug.

Anticonvulsants have both neurologic and systemic adverse effects. Dose-initiation adverse effects such as fatigue, dizziness, incoordination, and mental slowing are common in most patients and can be prevented with slow introduction of the drug. Dose-related effects may limit the use of a particular drug in a given patient. A dose-related adverse effect common to most drugs is cognitive impairment. Other neurologic adverse effects include cerebellar ataxia (phenytoin), diplopia (carbamazepine), tremor (valproic acid and lamotrigine), and chorea or myoclonus (phenytoin and carbamazepine). Idiosyncratic adverse effects are rare, unpredictable, severe, and sometimes life-threatening. Idiosyncratic and systemic adverse effects are listed in Table 61.3.

Many antiepileptic drugs are metabolized in the liver and are responsible for important drug interactions. The use of medications that are primarily metabolized hepatically should be avoided in patients with liver failure. Liver enzyme inducers (eg, carbamazepine, phenobarbital, phenytoin, primidone, oxcarbazepine, felbamate, and topiramate) increase metabolism and decrease the efficacy of oral contraceptives in preventing pregnancy. Valproic acid and felbamate are enzyme inhibitors and increase the levels of other anticonvulsants.

Special issues must be considered when managing epilepsy in pregnant patients. Seizure control is attempted first with monotherapy, with use of the lowest possible dose of anticonvulsant and monitoring of drug levels. Essentially all anticonvulsant drugs have the potential to cause developmental abnormalities. Valproic acid and, to a lesser extent, carbamazepine are selectively associated with an increased risk of neural tube defects.

KEY FACTS

- ✓ Management of seizure disorders—treatment of choice is monotherapy
- ✓ Dosage of drug used for treatment of seizure disorders—may be increased as high as necessary and to as much as can be tolerated
- ✓ Coadministration of antiepileptic drugs—has not been shown to have more antiseizure efficacy than the administration of only 1 drug without concurrently increasing toxicity
- ✓ Metabolism of antiepileptic drugs—many are metabolized in the liver and are responsible for important drug interactions; liver enzyme inducers increase metabolism and decrease the efficacy of oral contraceptives in preventing pregnancy
- ✓ Valproic acid and felbamate are enzyme inhibitors and increase the levels of other anticonvulsants

When to Start and Stop Anticonvulsant Therapy

Decisions about when to start and stop anticonvulsant therapy are difficult, and an easy, reliable algorithm simply does not exist. The decision to begin anticonvulsant therapy after a first seizure should be individualized for each patient. The decision depends on the risk of additional seizures, the risk of seizure-related injury, the loss of employment or driving privileges, and other psychosocial factors. An important decision is whether a single generalized tonic-clonic seizure is provoked by,

Table 61.3 • Systemic Adverse Effects of Antiepileptic Drugs

Adverse Effect	Drug Most Commonly Involved
Rash, Stevens-Johnson syndrome	10% risk with lamotrigine, CBZ, or PHT; 5% risk with other AEDs; lowest risk with VPA *Note*: Topiramate and zonisamide are contraindicated for patients with allergy to sulfa drugs
Liver failure	Highest risk with VPA and felbamate Risk increased in infants with mental retardation and receiving polytherapy or with underlying metabolic disease or poor nutritional status *Note*: benzodiazepines, carbamazepine, felbamate, phenytoin, phenobarbital, primidone, rufinamide, and valproic acid are primarily metabolized hepatically and should be avoided in patients with liver failure
Bone marrow suppression	Highest risk with felbamate and CBZ
Gum hypertrophy, hirsutism, acne, osteoporosis	Phenytoin
Weight gain, hair loss, tremor	VPA
Weight loss	Felbamate, topiramate
Headache, insomnia	Felbamate
Behavioral and cognitive disturbances	Barbiturates, benzodiazepines, topiramate, levetiracetam
Kidney stones	Topiramate, zonisamide
Hyponatremia	CBZ, oxcarbazepine
Atrioventricular conduction defect	CBZ, PHT
Neural tube defect	VPA more likely than CBZ, but all AEDs are potentially teratogenic

Abbreviations: AED, antiepileptic drug; CBZ, carbamazepine; PHT, phenytoin; VPA, valproic acid.

Box 61.1 • Risk Factors for Recurrence After the First Seizure

- Older than 60 years
- No precipitating factor identified (eg, no sleep deprivation or alcohol use)
- Focal seizure
- Abnormal findings on neurologic examination
- Abnormal electroencephalogram (spikes or focal slowing)
- Abnormal findings on imaging study
- Other factors
  - Family history of seizures (in first-degree relative)
  - History of febrile seizures
  - Onset during sleep
  - Postictal Todd paralysis
- Occupational risk

for example, sleep deprivation, alcohol, or concurrent illness. After the first seizure, the risk of recurrence ranges from 30% to 60%, and risks are higher for patients with abnormal EEG results and an identifiable cause (Box 61.1). After a second seizure, the risk of recurrence increases to 80% to 90%.

For many patients who have been seizure free for 1 to 2 years, anticonvulsant therapy can be discontinued. The benefit of discontinuing therapy should be weighed against the possibility of seizure recurrence and its potential adverse consequences. In adults, relapse occurs in 26% to 63% of patients within 1 to 2 years after therapy is discontinued. Predictors of relapse are an abnormal EEG before or during medication withdrawal, abnormal findings on neurologic examination, frequent seizures before remission, or mental retardation. To lessen the chance of seizures after discontinuing therapy, withdrawal should not proceed faster than a 20% reduction in dose every 5 half-lives.

Anticonvulsant Blood Levels

Anticonvulsant blood levels can be readily measured to help attain the best control of seizures. Therapeutic levels are represented by a bell-shaped curve, and patients with well-controlled seizures are included under that curve. Seizures are well controlled in many patients who have anticonvulsant blood levels below or above the therapeutic range. The anticonvulsant dose should *never* be changed on the basis of blood levels alone because toxicity is a clinical phenomenon, *not* a laboratory phenomenon. Measurement of anticonvulsant blood levels can be used to ensure that patients are taking their medication and to help determine whether new symptoms might be related to toxicity from the medication.

If a patient is receiving therapy for epilepsy and has breakthrough seizures, several factors should be considered, including the following:

1. Compliance issues
2. Excessive use of alcohol or other recreational drugs
3. Psychologic and physiologic stress (eg, anxiety or lack of sleep)
4. Systemic disease of any type, organ failure of any type, or systemic infection
5. A new cause of seizures (eg, neoplasm)
6. Newly prescribed medication, including other anticonvulsants (ie, polypharmacy) and over-the-counter drugs
7. Toxic levels of anticonvulsants (with definite clinical toxicity)
8. Nonepileptic spells (eg, psychogenic spells)
9. Progressive central nervous system lesion not identified previously with neuroimaging or lumbar puncture

Confirm diagnosis by observing seizure activity

↓

Administer oxygen; control airway; evaluate for intubation
Obtain and record vital signs; establish ECG recording
Obtain IV access; keep open with 0.9% saline
Draw venous blood for glucose, chemistry panel, hematology, toxicology, and antiepileptic drug levels
Determine arterial blood gases

↓

Administer 100 mg of thiamine IV and then 50 mL of 50% dextrose IV

↓

Administer IV lorazepam (0.1 mg/kg per dose, up to 4 mg per dose; may repeat dose once) or
IV diazepam (0.15-0.2 mg/kg per dose, up to 10 mg per dose; may repeat dose once) or
IM midazolam as a single dose (10 mg for >40 kg; 5 mg for 13-40 kg)

↓

Load with IV fosphenytoin (20 mg/kg, up to a phenytoin equivalent of 150 mg/min)

↓

If status persists after 20 mg/kg of fosphenytoin, give additional drug up to a maximum of 30 mg/kg

↓

If status persists, transfer patient to ICU because intubation, ventilation, or vasopressor may be needed
Phenobarbital 20 mg/kg IV, up to 60 mg/min
If status persists, give general anesthesia with pentobarbital, midazolam, or propofol

Figure 61.1. *Algorithm for the Management of Status Epilepticus. ECG indicates electrocardiographic; ICU, intensive care unit; IM, intramuscular; IV, intravenous.*

If no cause is found, the anticonvulsant dosage must be readjusted or the drug replaced with another.

Status Epilepticus

Status epilepticus is a medical emergency and a life-threatening condition. It can be defined by the duration of the seizure (eg, >5 minutes) or by whether repetitive seizures occur without recovery between seizures. The most common causes of status epilepticus include stopping the use of an anticonvulsant, alcohol toxicity or withdrawal, recreational drug toxicity, and central nervous system trauma or infection. Rarely, status epilepticus is the initial presenting sign of epilepsy. The management of status epilepticus is summarized in Figure 61.1.

Nonconvulsive status epilepticus may cause an acute confusional state or stupor and coma, especially in the elderly, and patients often have very subtle rhythmic motor activity in the limbs or face. EEG is a critical diagnostic tool because nonconvulsive status epilepticus must be treated as quickly and as vigorously as convulsive status epilepticus.

KEY FACTS

- ✓ Risk of recurrence of seizure—30%-60% after the first seizure; risks are higher for patients with abnormal EEG results and an identifiable cause; risk increases to 80%-90% after a second seizure
- ✓ Blood levels of anticonvulsants—the anticonvulsant dose should *never* be changed on the basis of blood levels alone
- ✓ Status epilepticus—a medical emergency and a life-threatening condition; can be defined by the duration of the seizure (eg, >5 minutes) or by whether repetitive seizures occur without recovery between seizures
- ✓ Nonconvulsive status epilepticus—may cause an acute confusional state or stupor and coma, especially in the elderly, and patients often have very subtle rhythmic motor activity in the limbs or face; EEG is a critical diagnostic tool because the condition must be treated as quickly and as vigorously as convulsive status epilepticus

62 Spinal, Peripheral Nerve, and Muscle Disorders

LYELL K. JONES JR, MD; BRIAN A. CRUM, MD

Diseases affecting the spinal cord, peripheral nerves, and skeletal muscles are common in clinical practice. These conditions may occur in isolation or as an associated feature (or complication) of nonneurologic disease. The clinical history and examination are useful for establishing a tentative diagnosis, which can be firmly established with diagnostic testing. Electrodiagnostic testing (nerve conduction studies and electromyography [EMG]) is the most useful method for adjunctive evaluation of patients with suspected nerve or muscle disease. Treatments are targeted to the underlying mechanism of disease.

Disorders of the Spine

Myelopathy

Spinal cord dysfunction, or *myelopathy*, may cause motor, sensory, or sphincter disturbances at or below the level of the spinal cord lesion. Myelopathy frequently results in muscle weakness, which typically occurs in the arms and legs if the lesion is at the cervical level or only in the legs if the lesion is below the lower cervical level. An upper motor neuron pattern weakness (elbow and wrist extensors and interosseous muscles in the upper limbs; hip flexors, knee flexors, and foot dorsiflexors in the lower limbs) is present and often bilateral. Patients frequently have sensory symptoms in the affected extremities and bowel and bladder difficulties. Other findings on examination include spasticity and increased muscle stretch reflexes below the level of the lesion. Extensor plantar reflexes (Babinski signs) may also be elicited. Sensory findings are often noted, and a sensory level can be a very powerful localizing finding on clinical examination. Extramedullary cord lesions are usually heralded by radicular pain. Intramedullary cord lesions are usually painless but may cause an ill-described nonlocalizable pain, sensory dissociation, and sacral sparing. Conus medullaris lesions are often characterized by "saddle anesthesia" and early involvement of the urinary bladder. Selected causes of myelopathy are listed in Box 62.1.

Patients suspected of having myelopathy require thorough evaluation. The relevant portion of the spinal cord should be evaluated with magnetic resonance imaging (MRI), and contrast medium should be administered if possible. Patients who are not candidates for MRI (because of body habitus, claustrophobia, or implanted devices) may undergo computed tomographic (CT) myelography, with the understanding that structural or compressive lesions may be recognized but intrinsic abnormalities in the spinal cord will not be apparent. In patients who do not have an apparent structural cause of myelopathy, a complete review for predisposing conditions must be performed. Cerebrospinal fluid (CSF) examination is particularly useful for identifying inflammatory, infectious, and neoplastic spinal cord disorders. Treatment is targeted to the identified cause. Inflammatory disorders of the spinal cord (as may occur with multiple sclerosis, neuromyelitis optica, sarcoid, or others) may respond to high-dose parenteral corticosteroids or other immunomodulatory therapies. All patients with myelopathy should have careful physiatric monitoring for mobility safety, bowel and bladder regimens, and spasticity management as indicated.

Cervical Spondylosis

Cervical spondylosis, or degenerative joint disease of the cervical spine, is common and may cause myelopathy (if the degenerative changes result in compression of the spinal cord) or cervical radiculopathy (if a cervical root is compressed). MRI is the preferred imaging study for patients suspected of having cervical spondylosis.

Box 62.1 • Causes of Myelopathy

- Spinal cord infarction (eg, from vasculitis)
- Spinal cord vascular malformation (cavernous malformation, arteriovenous malformation, dural arteriovenous fistula)
- Spinal epidural abscess or osteomyelitis with compression
- Tuberculoma
- Infectious myelitis
  - Viral: *Enterovirus* (polio), *Flavivirus* (West Nile), herpesvirus, CMV, varicella-zoster virus, EBV, HIV, HTLV-1, hepatitis A virus
  - Bacterial: *Treponema pallidum, Mycoplasma pneumoniae, Mycobacterium tuberculosis*, neuroborreliosis, dengue, *Bartonella henselae*, Whipple disease
  - Fungal
  - Parasitic: schistosomiasis, cysticercosis, hydatid disease
- Idiopathic transverse myelitis
- Multiple sclerosis
- Neuromyelitis optica
- Neurosarcoidosis
- Sjögren syndrome
- Systemic lupus erythematosus
- Behçet disease
- Scleroderma
- Postvaccinal or postinfectious
- Tumors (metastasis, ependymoma, neurofibroma, meningioma, astrocytoma)
- Paraneoplastic (antibodies to CRMP-5, amphiphysin IgG)
- Vitamin B_{12} or folate deficiency
- Vitamin E deficiency
- Copper deficiency or zinc toxicity (medications or supplements with zinc; denture cream)
- Superficial siderosis
- Nitrous oxide toxicity
- Syringomyelia or hematomyelia
- Cervical spondylosis
- Hereditary spastic paraplegia
- Adrenomyeloneuropathy
- Trauma
- Radiation injury

Abbreviations: CMV, cytomegalovirus; CRMP, collapsin-response mediator protein 5; EBV, Epstein-Barr virus; HTLV-1, human T-lymphotropic virus 1; IgG, immunoglobulin G.

Box 62.2 • Clinical Features of the Lateral Recess Syndrome

- Radicular pain is unilateral or bilateral with paresthesias in the distribution of L5 or S1
- Pain is provoked by standing and walking and is relieved by sitting
- Results of the straight leg–raising test are usually negative
- Little or no back pain

Lumbar Spine Disease

Asymptomatic bulging disks in the lumbar spine are common after the age of 30 years and are generally unlikely to cause nerve root compression. Bulging disks appear round and symmetric on imaging studies compared with herniated disks, which appear angular and asymmetric and extend outside the disk space. The criteria for surgical treatment of lumbar disk herniations include progressive reflex, sensory, or motor deficits or intractable pain after 6 to 8 weeks of conservative treatment.

The *lateral recess syndrome* is usually caused by an osteophyte on the superior articular facet; its features are summarized in Box 62.2. *Lumbar spinal stenosis* is most frequently caused by degenerative changes in the lumbar spine resulting in encroachment on multiple lumbosacral nerve roots. Its features are summarized in Box 62.3. Decompressive operations for lumbar stenosis have high initial success rates, although about 25% of patients become symptomatic again within 5 years.

Musculoskeletal low back pain (without leg pain) is treated best with a formal program of physical therapy and exercise, weight reduction, and education on postural principles.

Radiculopathy

Nerve root lesions (*radiculopathies*) usually are characterized by pain that is lancinating, follows a dermatomal or myotomal pattern, and is worsened by increasing intraspinal pressure (eg, sneezing or coughing) or by stretching of the nerve root. Radiculopathies may occur at any spinal level but are most common in the lumbosacral and cervical segments. Paresthesias and pain occur in a dermatomal pattern. Findings are in the root distribution and include weakness, sensory impairment, and decreased muscle stretch reflexes. Radiculopathies have many causes, including compressive lesions (eg, osteophytes, ruptured disks, and neoplasms) and noncompressive lesions (eg, postinfectious and inflammatory radiculopathies and

Box 62.3 • Clinical Features of Lumbar Spinal Stenosis

- Most patients are older than 50 years
- Neurogenic intermittent claudication (pseudoclaudication)
- Symptoms are usually bilateral but can be asymmetric or unilateral
- Pain usually has a dull, aching quality
- Whole lower extremity is generally involved
- Pain is provoked while walking or standing
- Sitting or leaning forward provides relief

metabolic radiculopathies, as in diabetes mellitus). Treatment is targeted to the underlying cause of the radiculopathy.

Motor Neuron Disease

Amyotrophic Lateral Sclerosis

Degenerative disorders that affect the motor neurons in the cerebral cortex and the anterior horn cells are called **motor neuron diseases**. The most common is amyotrophic lateral sclerosis (ALS). This disorder should be considered in any patient who has progressive, painless weakness. Typically, patients present with asymmetric weakness that begins distally and is associated with cramps and fasciculations. Footdrop and hand weakness are the most common first complaints. Often the initial (but incorrect) diagnosis is stroke, radiculopathy, carpal tunnel syndrome, or ulnar neuropathy. The diagnosis is often delayed. Bulbar weakness (eg, dysarthria more so than dysphagia) can be the presenting problem and is always present eventually. Bowel and bladder difficulties are very uncommon, and sensory abnormalities are rare. Findings on examination include weakness, atrophy, fasciculations, spasticity, and abnormal muscle stretch reflexes and extensor plantar responses. The hallmark is the mixture of upper motor neuron signs and lower motor neuron signs. Because of the progressive weakness affecting the limbs, bulbar muscles, and diaphragm, the disease is devastating, and patients have an average life span of about 3 years after the onset of symptoms.

Key Definition

Motor neuron diseases: *degenerative disorders that affect the motor neurons in the cerebral cortex and the anterior horn cells.*

ALS is an uncommon disease that is sporadic in 80% to 90% of patients. Several genes have been implicated in familial ALS, including *SOD1* and *C9orf72*. No drug has been effective in reversing the progressive course of this disease. Treatment with riluzole provided a 3-month survival benefit in a randomized controlled clinical trial, and intravenous edaravone modestly slowed the progression in select patients with early ALS. Riluzole and edaravone are the currently approved medications for the treatment of ALS. Management of ALS focuses on rehabilitation issues, nutrition, mobility, and communication; a multidisciplinary approach is useful.

Multifocal Motor Neuropathy

Multifocal motor neuropathy is a rare syndrome of purely lower motor neuron weakness that can mimic ALS. Treatment of multifocal motor neuropathy with intravenous immunoglobulin (IVIG) can effectively slow the progression of weakness, which is often distal, asymmetric, and accompanied by motor conduction block on nerve conduction studies and EMG and may be associated with high titers of serum antibodies to GM1 gangliosides.

Spinobulbar Muscular Atrophy

Spinobulbar muscular atrophy (also known as Kennedy disease) is a pure lower motor neuron degenerative process caused by an X-linked CAG repeat expansion in the androgen receptor gene. This most commonly affects elderly men and also leads to gynecomastia, diabetes mellitus, and a sensory peripheral neuropathy. Genetic testing is widely available. Although no effective treatment exists, the disease progresses much more slowly than ALS.

KEY FACTS

- ✓ Myelopathy—frequently results in muscle weakness, typically in the arms and legs if the lesion is at the cervical level or only in the legs if the lesion is below the lower cervical level
- ✓ Criteria for surgery of lumbar disk herniations—progressive reflex, sensory, or motor deficits or intractable pain after 6-8 weeks of conservative treatment
- ✓ Best treatment of musculoskeletal low back pain (without leg pain)—physical therapy and exercise, weight reduction, and education on postural principles
- ✓ Indications of nerve root lesions (radiculopathies)—pain that is sharp and lancinating, follows a dermatomal or myotomal pattern, and is worsened by increasing intraspinal pressure (eg, sneezing or coughing) or by stretching the nerve root
- ✓ Examination findings in ALS—weakness, atrophy, fasciculations, spasticity, and abnormal muscle stretch reflexes and extensor plantar responses; hallmark finding is the mixture of upper motor neuron signs and lower motor neuron signs

Peripheral Nerve Disorders

Peripheral nerve disorders may occur in patterns ranging from diffuse to focal and can be unimodal or multimodal in affected functions (eg, motor, sensory, or autonomic). Patterns of peripheral nerve disease and common causes are summarized in Table 62.1.

Length-Dependent Sensorimotor Peripheral Neuropathy

The most common pattern of peripheral nerve dysfunction is *length-dependent sensorimotor peripheral neuropathy* (the term is used interchangeably with *peripheral neuropathy* in this

Table 62.1 • Patterns of Neuropathy and Their Causes

Pattern of Neuropathy	Common or Important Causes
Length-dependent distal (stocking-and-glove) sensorimotor neuropathy	Diabetes mellitus Alcohol abuse Uremia Toxins (hexacarbons) Hereditary neuropathy Vitamin B_{12} deficiency Hypothyroidism Copper deficiency
Acute motor polyradiculoneuropathy	AIDP (Guillain-Barré syndrome) Lyme disease HIV neuropathy Porphyria Toxins (arsenic, thallium) Carcinomatous or lymphomatous meningitis
Chronic motor or sensorimotor polyradiculopathy	CIDP Paraproteinemia (eg, osteosclerotic myeloma) Hereditary neuropathy (eg, Charcot-Marie-Tooth disease) Lead toxicity Diabetes mellitus Amyloidosis
Sensory ataxic neuropathy	Sjögren syndrome Paraneoplastic disorder Diabetes mellitus Paraproteinemia Vitamin B_{12} deficiency HIV infection Cisplatin Vitamin B_6 excess Hereditary neuropathy
Painful peripheral neuropathy	Diabetes mellitus Vasculitis Hereditary amyloidosis Toxins (arsenic, thallium) Hepatitis C Cryoglobulinemia HIV neuropathy CMV polyradiculoneuropathy in HIV-positive patients Alcoholism Fabry disease
Neuropathy with prominent autonomic involvement	Acute or subacute Guillain-Barré syndrome Subacute pandysautonomia Paraneoplastic pandysautonomia Porphyria Vincristine neuropathy Botulism Chronic Diabetes mellitus Amyloidosis Sjögren syndrome
Mononeuropathy	Compressive neuropathy Idiopathic Tumor Trauma Diabetes mellitus HNPP
Mononeuropathy multiplex	Diabetes mellitus Vasculitis Lyme disease HIV neuropathy Sarcoidosis Leprosy Multifocal motor neuropathy HNPP

Abbreviations: AIDP, acute inflammatory demyelinating polyradiculoneuropathy; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CMV, cytomegalovirus; HNPP, hereditary neuropathy with liability to pressure palsies.

discussion). Peripheral neuropathies are usually characterized by distal weakness and distal sensory changes, and usually axonal loss predominates over demyelination. Peripheral neuropathies are typically symmetric and more severe in the legs than in the arms. Clumsy gait is often associated with distal numbness and paresthesias or footdrop. Examination findings include distal weakness, sensory loss, atrophy, and, sometimes, fasciculations. Muscle stretch reflexes usually are decreased. The evaluation of peripheral neuropathy is summarized in Box 62.4. A mechanism for the neuropathy can be identified in 70% to 80% of patients. A high percentage of patients referred to specialty centers for "idiopathic neuropathy" actually have hereditary neuropathies. On examination, the finding of high arches (ie, pes cavus) or low arches (ie, pes planus) with hammertoe deformities is a clue to a long-standing or hereditary neuropathy. Also, examination or close questioning of family members may secure a diagnosis.

Acute Inflammatory Demyelinating Polyradiculoneuropathy

A progressive neuropathy of rapid onset that affects both distal and proximal nerves suggests acute inflammatory demyelinating polyradiculoneuropathy (AIDP) (also called Guillain-Barré syndrome). The weakness and paresthesias ascend over several days, often accompanied by severe back pain. On examination, muscle stretch reflexes are absent. Patients may have respiratory muscle weakness, cranial neuropathy (particularly facial palsy, which can be bilateral), and autonomic instability. Typically AIDP is associated with an increased CSF protein concentration but no pleocytosis (cytoalbuminologic dissociation). The characteristic nerve conduction study and EMG findings are

Box 62.4 • Evaluation of Peripheral Neuropathy

- Basic laboratory investigations
  - CBC with platelet count
  - Erythrocyte sedimentation rate
  - Fasting blood glucose
  - Serum electrolytes
  - Serum creatinine
  - Liver function tests
  - Serum and urine electrophoresis and immunoelectrophoresis
  - Urinalysis
  - Chest radiography
  - Electromyography
  - Thyroid function test
  - Vitamin B_{12}
- Special investigations in selected patients
  - Vitamin E
  - Cholesterol and triglycerides
  - HIV serology
  - Lyme serology
  - Hepatitis serology
  - Cryoglobulins
  - Angiotensin-converting enzyme
  - Antineutrophil cytoplasmic antibodies
  - Antinuclear antibodies
  - Antibodies against extractable nuclear antigens
  - Gliadin antibodies, endomysial and tissue transglutaminase antibodies
  - Paraneoplastic antibodies
  - GM1 ganglioside antibodies
  - Porphyrins
  - Heavy metal screen
  - Serum copper and ceruloplasmin
  - Autonomic function tests
  - Cerebrospinal fluid analysis (when inflammatory, infectious, or neoplastic disorder is suspected)
  - Sural nerve biopsy (when amyloidosis, vasculitis, or lymphoma is suspected)
  - Investigation for inborn errors of metabolism
  - Genetic studies
  - MRI of nerve roots or plexus

Abbreviations: CBC, complete blood cell count; MRI, magnetic resonance imaging.

conduction block and temporal dispersion. About 50% of patients have a mild respiratory or gastrointestinal tract infection 1 to 3 weeks before the neurologic symptoms appear. Also, the syndrome may develop in patients who have autoimmune disease or a lymphoreticular malignancy. This syndrome has no particular seasonal, age, or sex predilection. Either plasma exchange or IVIG is effective in AIDP. Corticosteroids are not effective. Attention must be paid to other complications of the disease: deep vein thrombosis, pain, constipation, back pain, tachyarrhythmias and hypertension, peptic ulcers, decubital ulcers, and accumulation of secretions in the respiratory tract and aspiration.

Chronic Demyelinating Neuropathies

Chronic, predominantly motor or sensorimotor neuropathies include chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), paraproteinemic neuropathies (eg, associated with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes [POEMS] syndrome; amyloidosis; or osteosclerotic myeloma), hereditary neuropathies, lead toxicity, and diabetes mellitus (which often has axonal features as well). Most of these neuropathies are length-dependent neuropathies, but occasionally patients have predominantly proximal weakness, which suggests AIDP, CIDP, or porphyria. In sharp contrast to its lack of success in AIDP, corticosteroid therapy works well in CIDP. Plasma exchange and IVIG are also effective.

Most neuropathies associated with monoclonal gammopathies are not associated with underlying lymphoproliferative disorders, but some are associated with multiple myeloma, POEMS syndrome, amyloidosis, lymphoma, or leukemia. Affected patients usually are older than 50 years and present with symmetric sensorimotor polyradiculoneuropathy early in the disease course. The CSF protein concentration is usually increased. Immunoglobulin (Ig)M is more common than IgG or IgA, and disease characterized by IgM is generally more resistant to treatment. Plasma exchange can be effective therapy. Other immunosuppressive therapy, such as IVIG and perhaps rituximab, may also be effective.

Sensory Ataxic Neuropathy

Sensory ataxic neuropathies are characterized by severe proprioceptive sensory loss, ataxia, and areflexia. Some neuropathies are due to peripheral nerve demyelination and others to selective loss of large dorsal root ganglion neurons. A predominantly sensory polyneuropathy suggests paraneoplastic disorder, Sjögren syndrome, diabetes mellitus, paraproteinemias, HIV infection, vitamin B_{12} deficiency, cisplatin toxicity, vitamin B_6 toxicity, or hereditary neuropathy.

Small Fiber Neuropathy

Some peripheral neuropathies affect predominantly the small-diameter nociceptive fibers or their dorsal root ganglion neurons and are characterized by severe burning pain distally in the extremities. The examination findings are normal except for the distal loss of pain and temperature sensation. Typical causes are diabetes mellitus, vasculitis, amyloidosis, toxins, hepatitis C, cryoglobulinemia, some HIV-associated neuropathies, and alcoholism. Randomized, double-blind, placebo-controlled studies of patients with diabetic neuropathy have shown that the following medications are helpful for neuropathic pain: amitriptyline, tramadol, gabapentin, pregabalin, and duloxetine. If these agents are not useful or if they lead to adverse effects, other useful medications include carbamazepine, lidocaine patch (5%), narcotics, lamotrigine, mexiletine, and venlafaxine.

Autonomic Neuropathy

Patients who have neuropathy with autonomic dysfunction may present with orthostatic hypotension, urinary bladder or bowel dysfunction, and sexual dysfunction. Autonomic neuropathy may occur in the context of more widespread neuromuscular syndromes, such as those seen with Guillain-Barré syndrome, acute pandysautonomia, paraneoplastic dysautonomia, porphyria, diabetes mellitus, amyloidosis, or familial neuropathy. The basis of isolated autonomic neuropathies is frequently autoimmune, paraneoplastic, or inherited. Diabetes mellitus is a common cause of autonomic neuropathy, often with a comorbid sensorimotor peripheral neuropathy. Autonomic neuropathies with a subacute onset typically have an autoimmune or paraneoplastic basis, and affected patients may have abnormal serum markers of neurologic autoimmunity, such as nicotinic acetylcholine receptor (nAChR) antibody, antineuronal nuclear antibody type 1 (ANNA-1), collapsin-response mediator protein 5 autoantibody (CRMP-5), or Purkinje cell cytoplasmic antibody (PCA).

Diabetic Neuropathy

Diabetes mellitus may result in various patterns of peripheral nerve dysfunction, ranging from focal to diffuse. Patients with cranial nerve III neuropathy usually present with sudden diplopia, eye pain, impairment of the muscles supplied by cranial nerve III, and relative sparing of the pupil. Compressive cranial nerve III lesions usually involve the pupil in the early stages. Painful diabetic neuropathies include cranial nerve III neuropathy, acute thoracoabdominal (ie, truncal) radiculopathies, acute distal sensory neuropathy, lumbosacral radiculoplexus neuropathy, and chronic distal small fiber neuropathy.

Acute or subacute muscle weakness can occur in various forms of diabetic neuropathy. Weakness, atrophy, and pain affect the pelvic girdle and thigh muscles (asymmetrically or unilaterally). This condition has been termed **diabetic lumbosacral radiculoplexus neuropathy** (previously described with various terms such as *diabetic amyotrophy*) and is due to microvasculitis of the nerve. A course of intravenous corticosteroids may speed the recovery and reduce the pain.

Key Definition

Diabetic lumbosacral radiculoplexus neuropathy: *a form of diabetic neuropathy characterized by muscle weakness, atrophy, and pain in the pelvic girdle and thigh muscles (asymmetrically or unilaterally) due to microvasculitis of the nerve.*

Mononeuropathy

Mononeuropathy is characterized by impairment of a single nerve. The usual cause is compression, as in compressive ulnar neuropathy at the elbow, compressive median neuropathy in the carpal tunnel, and compression of the peroneal nerve as it winds around the fibular head. Diabetes mellitus is a common predisposing factor in patients with multiple compression mononeuropathies.

The most common mononeuropathy is median neuropathy at the wrist, most often referred to as carpal tunnel syndrome. Patients typically present with chronic, bothersome hand paresthesia, characteristically caused by or exacerbated by sustained postures. Patients often report waking up with hand paresthesia, which resolves or improves with shaking or repositioning. The diagnosis of median neuropathy at the wrist can be confirmed with electrodiagnosis or ultrasonography. Treatment typically begins with wrist-extension splints worn while sleeping, although often surgical decompression is required.

Mononeuropathy Multiplex

Mononeuropathy multiplex consists of asymmetric involvement of several nerves either simultaneously or sequentially. It suggests such causes as trauma or compression, diabetes mellitus, vasculitis, Lyme disease, HIV neuropathy, cryoglobulinemia, sarcoidosis, leprosy, tumor infiltration, multifocal motor neuropathies, or hereditary neuropathy with predisposition to pressure palsies.

KEY FACTS

- ✓ Characteristics of peripheral neuropathies—distal weakness and distal sensory changes (usually axonal loss predominates over demyelination), symmetric, and more severe in the legs than in the arms
- ✓ “Idiopathic neuropathy”—a high percentage of patients have hereditary neuropathies; the finding of high arches or low arches with hammertoe deformities is a clue to long-standing or hereditary neuropathy
- ✓ AIDP—progressive neuropathy of rapid onset that affects both distal and proximal nerves and is preceded by mild respiratory or gastrointestinal tract infection in about 50% of patients
- ✓ Treatment of AIDP—plasma exchange or IVIG (corticosteroids are not effective)
- ✓ Characteristics of small fiber neuropathy—severe burning pain distally in the extremities; examination findings are normal except for the distal loss of pain and temperature sensation

Neuromuscular Junction Disorders

Patients with neuromuscular transmission disorders typically present with fluctuating weakness manifested as fatigable weakness in the limbs, eyelids (causing ptosis), tongue and palate (causing dysarthria and dysphagia), and extraocular muscles (causing diplopia). Three major clinical syndromes of the neuromuscular junction are myasthenia gravis, Lambert-Eaton myasthenic syndrome, and botulism. Sensation, muscle tone, and reflexes usually are normal except in Lambert-Eaton myasthenic syndrome, in which the muscle stretch reflexes are diminished and patients may have symptoms of autonomic insufficiency. Certain drugs may impair neuromuscular junction kinetics; for example, penicillamine can cause a syndrome that appears similar to myasthenia gravis. Several drugs adversely affect neuromuscular transmission and may exacerbate weakness in these disorders. They include aminoglycoside antibiotics, quinine, quinidine, procainamide, propranolol, calcium channel blockers, and iodinated radiocontrast agents.

Myasthenia Gravis

Myasthenia gravis (MG) usually occurs in young women and older men and is often heralded by diplopia, dysarthria, dysphagia, and dyspnea. The deficits are usually fatigable, worsening with repetitive contraction on examination or subjectively late in the day. However, muscle stretch reflexes, sensation, mentation, and sphincter function are normal. The diagnosis of MG is classically characterized by the detection of serum nAChR and the presence of decremental responses to repetitive electrical stimulation of motor nerves detected on EMG. Single-fiber EMG is the most sensitive test for the detection of MG and other defects of neuromuscular transmission. Administration of a short-acting acetylcholine esterase inhibitor (eg, edrophonium) can temporarily reverse weakness due to MG; this can be used as a diagnostic test (although it is prone to false-positive results). Acetylcholine receptor antibodies are rare in conditions other than MG (ie, they do not occur in patients with congenital MG and they occur in only about 50% of those with purely ocular MG). Some patients who have MG without acetylcholine receptor antibodies have muscle-specific kinase (MuSK) antibodies that are also diagnostic for MG. These patients may have more severe weakness, often bulbar, and may be more resistant to immunosuppressive treatment, although they tend to respond to rituximab. Of the 30% of patients who have MG without acetylcholine receptor antibodies, half have MuSK antibodies.

Treatment strategies for MG include the use of acetylcholinesterase inhibitors and immunomodulatory agents. Acetylcholinesterase inhibitors, such as pyridostigmine bromide, are often given as initial therapy for MG. This therapy provides symptomatic improvement for most patients. Thymectomy is recommended for selected patients younger than 60 years with generalized weakness and for all patients with thymoma. CT of the chest should be performed for all patients with MG to evaluate for thymoma. Prednisone is the most commonly used immunomodulatory agent, but initial administration of high doses may exacerbate the weakness in about 10% of patients. Plasma exchange and IVIG are effective short-term therapies for patients with severe weakness and are particularly useful for a recent exacerbation, for preoperative preparation, or for initiating corticosteroid therapy. Long-term immunomodulatory treatments include azathioprine, mycophenolate mofetil, cyclosporine, and methotrexate. Rituximab has also been used for refractory cases.

Lambert-Eaton Myasthenic Syndrome

Patients with Lambert-Eaton myasthenic syndrome often have proximal weakness in the legs and absent or decreased muscle stretch reflexes (sometimes reflexes are elicited after brief exercise). This syndrome usually is diagnosed in middle-aged men who often have vague complaints such as diplopia, impotence, urinary dysfunction, paresthesias, mouth dryness, and other autonomic dysfunction (eg, orthostatic hypotension). The syndrome is due to the presence of antibodies directed against presynaptic voltage-gated P/Q-type calcium channels. It often is associated with small cell lung carcinoma. Treatment is focused on the underlying malignancy, if present. Pyridostigmine can be helpful, as in MG. Patients may also respond to the potassium channel blocker 3,4-diaminopyridine and to immunomodulatory treatments, as used in MG.

Botulism

Botulism should be suspected when more than 1 person has a syndrome that resembles MG or when a patient has abdominal and gastrointestinal tract symptoms that precede a syndrome that resembles MG. Bulbar and respiratory weakness is common, and pupillary abnormalities are distinctive compared with findings in MG. Botulism occurs after the ingestion of improperly canned vegetables, fruit, meat, or fish contaminated with the exotoxin of *Clostridium botulinum*. Paralysis is caused by toxin-mediated inhibition of acetylcholine release from axon terminals at the neuromuscular junction. Although an antitoxin is available, treatment is mainly supportive and especially emphasizes respiratory monitoring for ventilatory failure.

Muscle Disorders

Patients with muscle disease typically present with symmetric proximal weakness (in legs more than arms) and with weakness of neck flexors and, occasionally, of cardiac muscle. Muscle stretch reflexes and sensory examination findings are usually normal. Patients often report that they have difficulty arising from a chair or raising the arms over the head. Some myopathies have more prominent distal involvement or result in peculiar patterns of weakness (eg, myotonic dystrophy, inclusion body myositis, and distal muscular dystrophies). In myotonic dystrophy, atrophy and weakness begin distally and in the face and especially in the sternocleidomastoid muscles. An interesting feature of this dystrophy is *contraction myotonia* (ie, normal contraction of muscle with slow relaxation). Tests for myotonia include striking the thenar eminence with a reflex hammer (looking for percussion myotonia) and shaking the patient's hand (noting that the patient cannot let go quickly).

Myopathy, a general term for muscle disease, may be an acquired or progressive hereditary disease. Progressive, genetically

Box 62.5 • Classification of Myopathies

- Dystrophic myopathies (childhood or adult onset; progressive)
- Congenital myopathies (congenital onset; slowly progressive or nonprogressive)
- Inflammatory myopathies
  - Infectious and viral—toxoplasmosis, trichinosis
  - Granulomatous—sarcoidosis
  - Idiopathic—polymyositis, dermatomyositis, necrotizing myopathy, IBM
  - Inflammatory myopathy with collagen vascular disease
- Metabolic myopathies
  - Glycogenoses
  - Mitochondrial disorders
  - Defects of fatty acid oxidation
  - Endocrinopathy
  - Steroid myopathy
- Periodic paralyses
- Toxic—statin drugs, emetine, chloroquine, vincristine
- Miscellaneous
  - Amyloidosis
  - Critical illness myopathy

Abbreviation: IBM, inclusion body myositis.

mediated myopathy resulting in muscle tissue destruction is called *dystrophy*. However, patients with a muscular dystrophy may not have a family history positive for muscle disease. A classification of myopathies is given in Box 62.5. The diagnosis of myopathy is based on the history and physical examination findings, increased levels of creatine kinase, EMG, muscle biopsy results, and selected genetic testing.

Inflammatory Myopathy

Inflammatory myopathies include polymyositis, dermatomyositis, necrotizing myopathy, and inclusion body myositis. Patients with inflammatory myopathies, especially dermatomyositis, may have an underlying malignancy. Necrotizing myopathy can also be associated with an underlying cancer or autoimmune disease or exposure to medications such as statins (see below). Muscle biopsy should be used to confirm the diagnosis of inflammatory myopathy, although the diagnosis may be suggested by the history and examination findings, increased serum levels of creatine kinase, and EMG results.

Inclusion body myositis occurs mainly in patients older than 60 years; they have asymmetric weakness of proximal and distal muscles, with a predilection for quadriceps, biceps, and deep finger flexors (this pattern is highly suggestive of inclusion body myositis). Inclusion body myositis is not associated with collagen vascular diseases or neoplasms, and the creatine kinase level may be normal or slightly increased. Inclusion body myositis does not respond to immunosuppression.

Prednisone is the cornerstone for treatment of other inflammatory myopathies such as polymyositis, dermatomyositis, and necrotizing myopathy. The most common pitfall in treating these conditions is treating with doses of prednisone that are too low and are given for an insufficient time. Dermatomyositis, unlike inclusion body myositis, responds to IVIG. In polymyositis, dermatomyositis, and necrotizing myopathy, other immunomodulatory agents (including azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, or cyclophosphamide) are indicated if relapse occurs while the prednisone dose is being tapered, if unacceptable adverse effects develop from prednisone, or if the patient does not have a response to prednisone or the response is slow. Plasma exchange is ineffective for polymyositis, dermatomyositis, and inclusion body myositis. A regular exercise program is important, and it has been shown that physical therapy and exercise are not detrimental to patients with myopathies.

Statin-Induced Myopathy

Statin drugs (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) may produce an acute necrotizing myopathy characterized by myalgia, weakness, myoglobinuria, and a marked increase in the level of creatine kinase. This toxic effect is potentiated by fibric acid derivatives and cyclosporine. A subacute to chronic myopathy can also occur with statins. Symptoms may include cramps and myalgias, occasionally with little or no muscle weakness or creatine kinase elevation. After use of the drug is discontinued, symptoms may persist for an unknown duration, which may be as long as 3 to 6 months. Also, in some patients, statins likely unmask a presymptomatic acquired or genetic myopathy. The myopathic symptoms may persist even after use of the statin medication has been discontinued. In some patients, the persistent symptoms may be attributable to anti-HMG-CoA reductase antibodies.

KEY FACTS

- ✓ Neuromuscular transmission disorders—fluctuating weakness manifested as fatigable weakness in the limbs, eyelids (ptosis), tongue and palate (dysarthria and dysphagia), and extraocular muscles (diplopia)
- ✓ Characteristics of MG—usually occurs in young women and older men, heralded by diplopia, dysarthria, dysphagia, and dyspnea
- ✓ Lambert-Eaton myasthenic syndrome—often associated with small cell lung carcinoma; treatment is focused on the underlying malignancy, if present
- ✓ Inflammatory myopathies—polymyositis, dermatomyositis, necrotizing myopathy, and inclusion body myositis; an underlying malignancy may be present
- ✓ Statin-induced myopathy—an acute necrotizing myopathy caused by statin drugs and characterized by myalgia, weakness, myoglobinuria, and a marked increase in creatine kinase

Steroid Myopathy

Occasionally, myopathic proximal muscle weakness develops in patients receiving long-term therapy with glucocorticoid medications. The serum creatine kinase level is often not increased in these patients, and electrodiagnostic abnormalities may be subtle or absent. Muscle biopsy findings are often unremarkable, and the diagnosis is often confirmed with observation of improvement after discontinuing steroid use.

Electrolyte Imbalance

Severe hypokalemia (potassium level <2.5 mmol/L) and hyperkalemia (potassium level >7 mmol/L) produce muscle weakness, as do hypercalcemia, hypocalcemia, and hypophosphatemia. Familial periodic paralysis of the hypokalemic, hyperkalemic, or normokalemic type consists of episodes of acute paralysis that last 2 to 24 hours and can be precipitated by a carbohydrate-rich meal or strenuous exercise; cranial or respiratory muscle paralysis does not occur. The diagnosis is difficult to establish and is based on the potassium levels during an attack, family history, EMG, and genetic testing for causative sodium and calcium channel mutations.

Endocrine Diseases

Hyperthyroidism and hypothyroidism, hyperadrenalism and hypoadrenalism, acromegaly, and primary and secondary hyperparathyroidism cause muscle weakness.

IX

Questions and Answers

Questions

Multiple Choice (Choose the best answer)

IX.1. A 74-year-old woman presents to the outpatient clinic for a general evaluation. She has a history of hyperlipidemia, hypertension, and type 2 diabetes mellitus, and she smokes cigarettes. What is the most important modifiable stroke risk factor to address for this patient?

a. Hyperlipidemia
b. Hypertension
c. Type 2 diabetes mellitus
d. Cigarette smoking

IX.2. An 85-year-old man presented with headache and left-sided weakness. Noncontrast computed tomography (CT) of the head showed a right frontal lobar intracerebral hemorrhage; results from CT angiography of the brain were normal. The patient takes warfarin for atrial fibrillation, and his international normalized ratio at presentation was 1.4. His medical history is notable for well-controlled hypertension and dementia. What is the most likely cause of the hemorrhage?

a. Hypertension
b. Warfarin
c. Cerebral amyloid angiopathy
d. Arteriovenous malformation

IX.3. A 33-year-old man with a history of episodic migraine presents to the emergency department with a severe headache that felt as if he had been hit in the back of the head with a bat. He reported that the attack reached peak severity in less than 1 minute. This is the worst headache of his life. What are the best next steps in headache diagnosis and management?

a. Computed tomography (CT) of the head, lumbar puncture, and, if results are negative, cerebrovascular imaging
b. CT of the head, lumbar puncture, and, if results are negative, sumatriptan subcutaneous injection
c. CT of the head and, if results are negative, sumatriptan subcutaneous injection
d. Lumbar puncture and, if results are negative, sumatriptan subcutaneous injection

IX.4. A 43-year-old woman has a long-standing history of migraine with and without aura. Recently, she has had a headache on at least 4 or 5 days per week. She estimates that at least 50% of the time she needs to retreat into a dark, quiet room and cannot eat or drink because of nausea. She uses zolmitriptan 5 mg nasal spray 2 times per week for the more severe attacks, and that medication is effective. She is not overusing medications because her treating physician has defined strict limitations. Therapy with amitriptyline, topiramate, and propranolol has failed. What is the best next step in management?

a. Nortriptyline
b. Valproic acid
c. OnabotulinumtoxinA injections
d. Sumatriptan

IX.5. A 63-year-old man presents with fluctuating vertigo, hearing loss, tinnitus, and ear pressure. He does not have headache, photophobia, or phonophobia. The episodes of vertigo are not necessarily triggered by positional changes. However, if he is already having an episode of vertigo, it is worsened with any movement. An audiogram demonstrates sensorineural hearing loss. Magnetic resonance imaging of the brain shows no abnormalities such as posterior fossa lesions. What is the best next step in treatment?

a. Sumatriptan
b. Canalith repositioning maneuvers
c. Short course of corticosteroids and antiviral medications
d. Salt restriction and diuretics

IX.6. A 23-year-old woman with a history of left optic neuritis at age 21 years presents with right hemiparesthesias. Magnetic resonance imaging (MRI) of the head shows 5 small, ovoid T2-weighted hyperintense lesions distributed in the pericallosal region and brainstem, 3 of which show enhancement with gadolinium. Cerebrospinal fluid (CSF) analysis shows 5 oligoclonal bands that were not present in the serum. The patient had already started to notice improvement in symptoms before the appointment with her neurologist, but the symptoms resolved after corticosteroid therapy. Why is multiple sclerosis (MS) the most likely diagnosis?

a. The patient is a woman.
b. One specific diagnostic biomarker was present.
c. The disease was disseminated in time and space.
d. The symptoms improved with corticosteroids.

IX.7. A 23-year-old woman with a history of left optic neuritis at age 21 years presented with right hemiparesthesias. Magnetic resonance imaging of the head and cerebrospinal fluid analysis showed typical multiple sclerosis (MS) findings. Her symptoms resolved after corticosteroid therapy. The clinical team diagnosed MS and recommended immunomodulatory therapy to prevent relapses. The patient wants to review the adverse effects of the various drug options. Bradycardia and heart block are recognized adverse effects of which of the following immunomodulatory therapies?

a. Fingolimod
b. Interferon beta
c. Natalizumab
d. Alemtuzumab

IX.8. A 65-year-old man is evaluated for a 6-year history of progressive tremor. He has a background history of type 2 diabetes mellitus, diabetic peripheral neuropathy, hypothyroidism (he receives thyroid hormone replacement therapy), and arthritis. He first noticed a tremor in his right hand; 1 year later, his left hand also had a tremor. He noticed the tremor when he was holding the newspaper or drinking coffee. His handwriting is less tidy. About a year ago, his wife noticed that his head shakes occasionally. He does not drink alcohol, so the effect of alcohol on the tremor is unknown. He thinks his balance is a little worse and his walking is slower. He feels stiff all over, particularly in the morning. His brother had Parkinson disease, but there is no family history of tremor. On neurologic examination, he had a hint of rest tremor in the right thumb. With arm posture and finger-nose maneuvers, there is moderate asymmetric tremor in the right upper limb (more pronounced than in the left upper limb). He has a no-no type head tremor. He has gegenhalten tone in his arms but no definite rigidity. He does not have bradykinesia on examination. His gait is slowed with an erect posture, and he has a normal arm swing. Retropulsion testing shows normal balance. The Romberg test is mildly positive. Reflexes are depressed throughout. Vibration is impaired in the lower limbs, and response to light touch is absent in the feet. Sensation is normal in the upper limbs. Thyroid function is normal. What is the most likely diagnosis?

a. Essential tremor
b. Parkinson disease
c. Enhanced physiologic tremor due to thyroxine
d. Neuropathic tremor

IX.9. A 60-year-old woman is evaluated for progressive gait difficulties and falls in the past 10 months. The initial diagnosis was Parkinson disease, and she received levodopa therapy with mild improvement of the symptoms for 3 months, but then she had a lack of response and orthostatic dizziness. Urinary urgency developed and, more recently, urinary incontinence. She denies any cognitive symptoms. Neurologic examination showed normal mental status, including attention and construction abilities, normal eye movements, bradykinesia, rigidity, severe gait instability with a tendency to fall backward, mild dysmetria, and jerky movements of the upper limbs. Motor strength, sensory examination, and reflexes were normal. Blood pressure in the supine position was 150/90 mm Hg with a heart rate of 80 beats per minute. Standing blood pressure was 90/60 mm Hg with a heart rate of 84 beats per minute. Polysomnography showed absent muscle atonia during rapid eye movement (REM) sleep and laryngeal stridor. Ultrasonography of the bladder showed a post-void residual volume of 300 mL. Which is the most likely diagnosis?

a. Dementia with Lewy bodies
b. Progressive supranuclear palsy
c. Corticobasal degeneration
d. Multiple system atrophy

IX.10. A 17-year-old boy is evaluated for progressive gait difficulties, slurred speech, and upper extremity tremor over the past 2 years. During the past year he has had difficulties with performance at school, and increased irritability. Examination shows fluctuating level of attention, masked faces, broad-based and shuffling gait, rigidity, upper extremity tremor at rest with marked worsening with voluntary movements, and mild dysmetria. Motor strength, sensory examination findings, and reflexes are normal. What is the first diagnosis to be considered in this patient?

a. Juvenile Parkinson disease
b. Dopa-responive dystonia
c. Wilson disease
d. Friedreich ataxia

IX.11. A 45-year-old woman comes into the emergency department with weakness and shortness of breath. Her symptoms have been present for 2 days but have worsened today to the point that she became alarmed. On examination, the patient is dyspneic and has difficulty keeping her eyelids open, although she is fully awake and conscious. In addition, she has a diffuse general pattern of weakness that worsens as you ask her to exert herself on examination. What is the most likely diagnosis for this patient?

a. Myasthenia gravis from thymoma
b. Cervical intramedullary cord compression from metastatic breast cancer
c. Toxic-metabolic encephalopathy from adenocarcinoma of the lung
d. Limbic encephalitis from an autoimmune disease

IX.12. A 75-year-old man was hospitalized with new-onset seizures. After his condition was stable, magnetic resonance imaging of the brain with and without a contrast agent showed a heterogeneously enhancing 3-cm mass in the right frontal lobe with surrounding vasogenic edema. Dexamethasone was started along with antiepileptic therapy. What is the best next step in management?

a. Consult the neurosurgery service about the possibility of resection and tissue diagnosis.
b. Consult the medical oncology service about intrathecal chemotherapy.
c. Consult the laboratory medicine service about beginning intravenous immunoglobulin.
d. Consult the palliative medicine service for hospice care.

IX.13. A 55-year-old lifelong nonsmoker has received a diagnosis of adenocarcinoma of the lung. He presents with severe low back pain and urinary retention. What is the most likely diagnosis?

a. Brain metastases
b. Paraneoplastic disorder
c. Epidural cord compression
d. Toxic metabolic encephalopathy

IX.14. A 32-year-old woman with a history of depression is evaluated for recurrent episodes of gradual loss of awareness, falls, and whole body jerking, which waxes and wanes for 20 to 30 minutes. The frequency of the events has increased despite appropriate trials of 3 different antiepileptic drugs. The events are more frequent when she has emotional stress. Results were normal when routine awake and sleep electroencephalography (EEG) and magnetic resonance imaging (MRI) of the brain were performed 1 year ago. What is the best next step in management?

a. Another antiepileptic drug should be tried.
b. A routine EEG should be repeated.
c. MRI of the brain should be repeated.
d. A typical event should be recorded with prolonged video and EEG.

IX.15. A 75-year-old man with hepatitis C and chronic liver dysfunction has had 2 focal seizures with secondary generalization. Which of the following would be the best initial medication for this patient?

a. Carbamazepine
b. Phenobarbital
c. Phenytoin
d. Levetiracetam

IX.16. A 79-year-old woman with a past medical history of chronic obstructive pulmonary disease had her first seizure. Upon arrival at the emergency department 15 minutes later, she is confused and the left side of her face twitches intermittently. She has not received sedating medications. Results are normal for electrocardiography, blood glucose level, chemistry panel, and hematologic and toxicologic testing. Which of the following should be efficacious as the initial therapy for this patient?

a. Lorazepam intravenously (IV)
b. Levetiracetam orally
c. Fosphenytoin IV
d. Diazepam intramuscularly (IM)

IX.17. An 82-year-old man presents with neck pain that has worsened over the past 7 months. He has had burning hands during that time and occasional urinary incontinence since he underwent prostatectomy several years ago. On examination he has mild weakness throughout the upper limbs, moderate weakness of the iliopsoas and hamstring muscles in the lower limbs, and an unsteady gait. What is the best next step in management?

a. Urgent computed tomography (CT) of the cervical spine
b. Gabapentin therapy
c. Magnetic resonance imaging (MRI) of the cervical spine
d. Physical therapy

IX.18. A 53-year-old woman with diabetes mellitus has had pain in her right hand for the past 3 weeks. On examination she has weakness of the right thenar muscles and sensory loss over the ventrolateral portion of the hand. Magnetic resonance imaging (MRI) of her cervical spine shows mild diffuse degenerative changes. What is the best next step in management?

a. Gabapentin therapy
b. Carpal tunnel decompression
c. Cervical spinal decompression and fusion
d. Stellate ganglion block

IX.19. A 67-year-old man has had slowly progressive asymmetric weakness of distal and proximal muscles in all limbs over the past 3 years. He does not take any medications. He does not have any pain or other sensory symptoms. On examination, he has no rash. He has diffuse limb weakness that is most prominent in the finger flexor and quadriceps muscles. Muscle stretch reflexes are normal. What is the most likely diagnosis?

a. Length-dependent peripheral neuropathy
b. Amyotrophic lateral sclerosis
c. Inclusion body myositis
d. Myasthenia gravis

Answers

IX.1. Answer b.

Although all 4 choices are important modifiable risk factors that contribute to stroke risk and should be addressed as part of secondary stroke prevention, hypertension has the biggest impact on ischemic and hemorrhagic stroke prevention. Additional modifiable risk factors include obesity, obstructive sleep apnea, sedentary lifestyle, metabolic syndrome, and heavy alcohol consumption.

IX.2. Answer c.

Lobar hemorrhages in elderly patients are often secondary to cerebral amyloid angiopathy. Hypertension is the main risk factor for all intracerebral hemorrhages, but it usually affects deep penetrating vessels and causes hemorrhages in the basal ganglia, thalamus, brainstem, or cerebellum. Anticoagulant medications, such as warfarin, increase the risk of intracerebral hemorrhage for patients with cerebral amyloid angiopathy but are not the primary cause. An arteriovenous malformation would be unlikely given the normal findings with CT angiography of the brain.

IX.3. Answer a.

This patient is having a thunderclap headache, which reaches peak intensity in less than 1 minute and is a medical emergency. The most worrisome cause of a thunderclap headache is a subarachnoid hemorrhage; however, after a subarachnoid hemorrhage has been ruled out, other vascular and nonvascular causes should be considered before treatment. CT of the head should be performed as soon as possible, and then a lumbar puncture should be performed. If results from both the CT of the head and the lumbar puncture are negative, additional investigation, including cerebrovascular imaging, is recommended. Until vascular causes of thunderclap headache, such as reversible cerebral vasoconstriction syndrome, have been ruled out, triptan medications should not be used for empirical treatment because of the potential for vasoconstrictive complications.

IX.4. Answer c.

This patient meets criteria for chronic migraine because she is having 15 or more headache days per month with at least 8 days with migraine features, including photophobia, phonophobia, and nausea. OnabotulinumtoxinA injections (155 units every 12 weeks) are the only treatment approved by the US Food and Drug Administration for chronic migraine. In addition, several oral preventive medications for the treatment of migraine have failed to help this patient. Nortriptyline is the major active metabolite of amitriptyline, which failed to help, so nortriptyline would likely be ineffective. Valproic acid could be considered, but onabotulinumtoxinA injections are a better answer since this patient has chronic migraine. The patient's use of zolmitriptan 5 mg nasal spray is effective for attacks (similarly, sumatriptan would be expected to be effective for attacks), so that treatment regimen does not need to be changed, but her preventive treatment regimen needs to be optimized.

IX.5. Answer d.

This patient is presenting with Meniere disease. He has the classic characteristics of vertigo, sensorineural hearing loss, tinnitus, and aural fullness. Meniere disease is treated symptomatically with antiemetics and preventively with a low-salt diet (daily sodium intake of <2 g) and diuretics. Sumatriptan may be effective for vestibular migraine attacks but not for Meniere disease. Canalith repositioning maneuvers are effective for benign paroxysmal positional vertigo but not for Meniere disease. Corticosteroids and antivirals are often used for viral labyrinthitis but not for Meniere disease.

IX.6. Answer c.

Clinical and MRI data showed dissemination of abnormalities in time and space, a characteristic of MS. The disorder is more common in women, but it is frequently encountered in men also. One specific test is not available for making a diagnosis of MS. Clinical features, radiology, and CSF data can all assist in making the diagnosis. Recovery of symptoms may be accelerated by use of corticosteroid therapy, which is also true for other inflammatory central nervous system disorders, including autoimmune encephalitis and neurosarcoidosis.

IX.7. Answer a.

Bradycardia and heart block are recognized adverse effects of fingolimod therapy. Initial dosing should be done under supervision with monitoring of the heart rate.

IX.8. Answer a.

Hand tremor with posture and action is suggestive of essential tremor. In long-standing essential tremor, rest tremor may be present but is minimal in comparison with postural tremor. The presence of head tremor is also suggestive of essential tremor. A family history can be negative for patients with essential tremor. In contrast, tremor in Parkinson disease is more pronounced at rest than with posture or action. The patient does not have bradykinesia, which is a cardinal sign for the diagnosis of a parkinsonian disorder. Generalized stiffness and slowness can be attributed to other medical conditions in the absence of rigid tone and bradykinesia. The impaired balance likely reflects sensory ataxia due to peripheral neuropathy and not to postural instability in parkinsonism because of the normal retropulsion test results. Enhanced physiologic tremor is a fine, fast postural and action tremor confined to the hands and does not involve the head. Neuropathic tremor is a postural-action tremor of the limbs that occurs in the presence of peripheral neuropathy. The patient's diabetic neuropathy is confined to the feet, with normal upper limb sensory examination findings. This excludes an upper limb neuropathic tremor. In addition, neuropathic tremor is not associated with head tremor.

IX.9. Answer d.

The presence of levodopa-resistant parkinsonism, falls in the early course of the disease, mild dysmetria (suggestive of cerebellar dysfunction), jerky limb movements (myoclonus), orthostatic hypotension, urinary retention, and laryngeal stridor are all consistent with multiple system atrophy. Dementia with Lewy bodies would be less likely given the lack of attention and constructional impairment and no history of cognitive fluctuations or visual hallucinations. Progressive supranuclear palsy and corticobasal degeneration would be unlikely given the prominent autonomic features and the presence of REM sleep behavior disorder. In addition, the lack of impaired vertical eye movements would argue against progressive supranuclear palsy, and the lack of asymmetric apraxia, dystonia, or cortical sensory loss would argue against corticobasal degeneration.

IX.10. Answer c.

Wilson disease should always be considered for any young patient with a movement disorder with or without cognitive and behavioral symptoms. Wilson disease is an autosomal recessive disorder due to mutations of the gene encoding the copper transporter ATP7. Typical findings include the presence of copper deposits around the cornea, reduced plasma ceruloplasmin, and reduced plasma and urinary copper levels. Whereas dopa-responsive dystonia and juvenile-onset Parkinson disease should be considered in young patients with dystonia or parkinsonism, the cognitive and behavioral manifestations and cerebellar signs in this patient are not consistent with these disorders. Friedreich ataxia is characterized by not only severe ataxia but also proprioceptive sensory loss, areflexia, and bilateral Babinski sign, which are not present in this patient.

IX.11. Answer a.

This patient is presenting with an exacerbation of myasthenia gravis as a result of a thymoma. Serum studies looking for acetylcholinesterase antibodies and electromyography will confirm the suspected diagnosis. Resection of the thymoma is a priority in addition to consultation with the neurology service for medical management. The patient has no clinical features to suggest that a spinal or encephalopathic process is present.

IX.12. Answer a.

This patient most likely has a high-grade glioma. Tissue diagnosis is imperative to exclude mimics, such as multiple sclerosis, abscess, and solitary metastasis. Maximal surgical resection is recommended with subsequent chemotherapy in combination with radiotherapy. Hospice care would not be appropriate at this time.

IX.13. Answer c.

This patient is presenting with a cauda equina syndrome due to lower lumbar epidural cord compression. Back pain is the most common symptom in patients with cancer and epidural metastasis. Dexamethasone can be started immediately for symptom relief. The radiation oncology service should be consulted next for treatment and neurosurgery only if the patient's condition worsens during radiotherapy.

IX.14. Answer d.

Epileptic seizures are characterized by abrupt onset and offset and not gradual loss of awareness with intermittent movements. The duration of the events lasting 20 to 30 minutes is less typical for generalized tonic-clonic seizures. The patient has a history of depression, and triggers of emotional stress are risk factors for psychogenic nonepileptic events. The diagnosis of either seizure or psychogenic nonepileptic events should be confirmed with simultaneous video and EEG monitoring with the goal of recording a typical event. A trial with another antiepileptic drug would not be helpful for psychogenic nonepileptic events. Repeating a routine EEG, which is typically around 60 minutes, would likely not capture the symptoms of interest. Repeating MRI of the brain would be unlikely to help in the management of this patient when MRI findings were normal a year ago.

IX.15. Answer d.

Benzodiazepines, carbamazepine, felbamate, phenytoin, phenobarbital, primidone, rufinamide, and valproic acid are primarily metabolized in the liver and should be avoided in patients with hepatic failure.

IX.16. Answer a.

Nonconvulsive status epilepticus may cause an acute confusional state or stupor and coma, especially in the elderly. Patients may have subtle rhythmic motor activity in the limbs or face. Electroencephalography is a critical diagnostic tool because nonconvulsive status epilepticus must be treated as quickly and as vigorously as convulsive status epilepticus. Initial therapy for status epilepticus should include IV lorazepam, IV diazepam, or IM midazolam.

IX.17. Answer c.

This patient's clinical presentation is most consistent with a cervical myelopathy, and MRI of the cervical spine would be the diagnostic test of choice. Since the course of the disease is not acute, urgent CT of the cervical spine is not warranted and would offer less discrimination of the soft tissue than MRI. Gabapentin should be used with caution in the elderly. While physical therapy may be appropriate to improve this patient's gait and safety, establishing the diagnosis with MRI imaging is a better choice.

IX.18. Answer b.

This patient's clinical presentation is most consistent with compression of the right median nerve at the carpal tunnel. The best treatment is surgical decompression. A systemic therapy such as gabapentin would not be appropriate at this time in this patient. Given this patient's MRI findings and clinical syndrome, surgical decompression of the cervical spine would not be appropriate. Finally, stellate ganglion block is reserved for patients who have shoulder, upper arm, and chest pain that is refractory to other therapies.

IX.19. Answer c.

This patient's clinical syndrome is most consistent with inclusion body myositis. Supporting features include progressive weakness in all limbs, lack of pain, and prominence of the flexor muscles. This patient's presentation is not consistent with peripheral neuropathy, amyotrophic lateral sclerosis, or myasthenia gravis. Patients with peripheral neuropathy usually present with distal weakness and distal sensory changes that are typically symmetric and more severe in the legs than in the arms. Amyotrophic lateral sclerosis is a degenerative disorder that affects the motor neurons in the cerebral cortex and the anterior horn cells and causes progressive, painless weakness that typically begins distally. Patients with myasthenia gravis classically present with diplopia, dysarthria, dysphagia, and dyspnea that are usually worse with repetitive contraction on examination or subjectively late in the day.

Section X

Oncology

63 Breast Cancer[a]

TUFIA C. HADDAD, MD; TIMOTHY J. MOYNIHAN, MD

Magnitude of the Problem

In **the United** States, approximately 252,000 new cases of invasive breast cancer are diagnosed annually. Breast cancer is the most common cancer in women and develops in approximately 1 in 8 women who achieve a normal life expectancy. It is the second most common cause of cancer death among women in the United States (lung cancer is the most common). The incidence decreased in the early 2000s and has leveled off since then. Breast cancer mortality rates have steadily decreased since the mid 1990s because of improvements in systemic therapy and early detection.

Risk Factors

Risk factors for breast cancer are shown in Table 63.1. Breast cancer–associated genes (*BRCA1* and *BRCA2*) are found in 5% to 10% of cases of breast cancer, but the women who carry these genes have a 50% to 80% chance of breast cancer developing in their lifetime. Most cases of breast cancer are sporadic—less than 25% of women with breast cancer have familial or hereditary risk factors.

Screening

Screening Criteria

Routine screening of standard-risk, asymptomatic women for breast cancer has been shown to decrease the probability of dying of breast cancer. Most guidelines suggest beginning annual clinical breast examination and bilateral screening mammography at age 40 years, whereas others suggest biennial mammography beginning at age 50 years. For each woman, screening mammography should continue until she has a life expectancy of less than 10 years because of advanced age or comorbid conditions. Women with normal mammography findings and normal breast density should continue annual screening. Women with mammographically dense breasts have an increased risk of breast cancer as well as an increased risk of false-negative screening mammography and, thus, should be considered for supplemental screening modalities. Supplemental screening tests could include tomosynthesis, whole-breast ultrasonography, molecular breast imaging, or breast magnetic resonance imaging (MRI).

High-risk groups for whom annual screening with breast MRI is indicated include those with prior history of therapeutic radiation to the chest between ages 10 and 30 years; a known germline deleterious *BRCA1* or *BRCA2* mutation or a first-degree relative who is a *BRCA1* or *BRCA2* mutation carrier; a lifetime risk of approximately 20% to 25% or greater, as defined by BRCAPRO or other models that are largely dependent on family history; or other personal or first-degree family history of a mutation-associated, hereditary breast cancer syndrome. For these women, annual screening mammography is recommended along with complementary screening MRI.

Evaluation of Abnormal Screening Results

Women with abnormal results of screening mammography require further evaluation. The specific nature of follow-up depends on the screening findings. For calcifications or lesions with low suspicion of malignancy, short-term follow-up imaging is reasonable. Other findings that are more suspicious require additional diagnostic imaging or biopsy. Biopsy is the only definitive test for cancer.

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[a] Mayo Clinic does not endorse specific products or services included in this chapter.

Table 63.1 • Risk Factors for Breast Cancer

Risk Factor	High Risk (RR, >4.0)	Low to Moderate Risk (RR, 1-4)
Age	Advanced (≥65 years)	
Race		White
Endogenous hormones		Menarche before age 12 y Menopause after age 55 y Nulliparous Age >30 y at first full-term pregnancy
Exogenous hormones		Recent and long-term use of combined estrogen/progesterone menopausal hormone therapy
Personal medical history	*BRCA1* or *BRCA2* mutation History of breast cancer History of breast biopsy with benign proliferative changes with atypia, LCIS, or DCIS Heterogeneously or extremely dense breast tissue on mammography Prior history of chest radiotherapy	Obesity in postmenopausal women History of ovarian or endometrial cancer History of breast biopsy showing benign breast disease without atypia
Family medical history	First-degree family member with *BRCA1* or *BRCA2* mutation 2 first-degree family members with breast cancer Other rare familial syndromes associated with breast cancer	1 first-degree family member with premenopausal (RR, 3.3) or postmenopausal (RR, 1.8) breast cancer
Lifestyle		Moderate alcohol intake

Abbreviations: DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; RR, relative risk.

Palpable abnormalities—either self-detected or identified by clinical breast examination—should be followed up with diagnostic imaging, with consideration for mammography or ultrasonography. If suspicious characteristics are seen on imaging, these women should undergo biopsy for definitive diagnosis. If imaging results are negative and the palpable mass persists, referral to a breast surgeon is indicated.

Pathologic Characterization

Breast cancer, by definition, is invasive, with malignant cells penetrating from their site of origin within the breast into the surrounding stroma. In situ carcinomas of the breast are noninvasive, and they can be characterized as ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS). Of the invasive breast cancers, approximately 90% are classified as ductal or lobular carcinomas, which originate within the ducts and lobules of the normal breast (Figure 63.1).

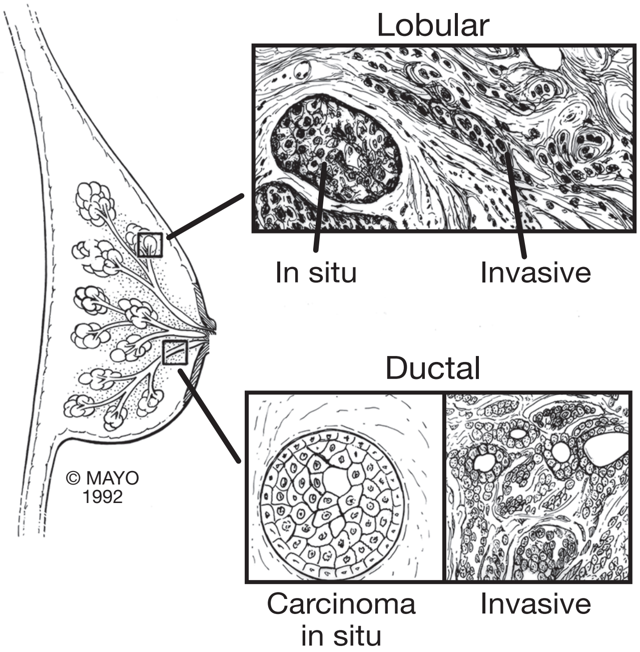

Figure 63.1. *Breast Carcinomas: Lobular and Ductal, In Situ and Invasive.*

DCIS is a precancerous lesion that, if left untreated, may progress to invasive disease. Whether DCIS should be considered a cancer (stage 0) is controversial. LCIS is not a precursor for invasive disease but rather is a marker for increased risk of future development of invasive carcinoma in the ipsilateral or contralateral breast. Women with LCIS have an estimated 2% annual risk of an eventual diagnosis of invasive breast cancer.

Invasive (also called infiltrating) ductal carcinoma is the most common histologic type (75% of breast cancers). Invasive lobular carcinoma accounts for 5% to 15% of breast cancers, is more frequently multifocal and bilateral, and is less likely to be seen on mammography. Invasive breast cancer has the potential for systemic spread, as opposed to carcinoma in situ, which does not have metastatic potential, because by definition, the malignant cells have not invaded through the basement membrane.

Natural History and Prognostic Factors

General Principles

The clinical outcomes for invasive breast cancer depend primarily on whether cancer cells have spread to other organs. No established tests can detect the presence of microscopic metastatic disease. The most important predictor of micrometastatic disease is lymphatic spread from the primary tumor to the ipsilateral axillary lymph nodes. Tumor grade and size, the presence or absence of lymph node involvement, hormone receptor status, and human epidermal growth factor receptor 2 (HER2) gene amplification or protein overexpression are the key prognostic factors for breast cancer. In addition, 2 molecular gene-expression assays are available that can provide individualized prognostic and predictive information to guide treatment decisions.

Hormone Receptor Status

Breast cancer cells may or may not express the hormone receptors estrogen receptor (ER) and progesterone receptor (PR). In general, given the same stage of disease, patients with ER-positive tumors have a better prognosis than those with ER-negative tumors. For patients with ER-positive breast cancer, the risk of relapse in the first 5 years after treatment is less than that for patients with ER-negative disease (because of the benefit from adjuvant endocrine therapy), and the risk slowly decreases but persists for several decades thereafter. The extent of ER expression may be important in treatment outcome; the greater the expression of tumor cells staining positive for ER, the more likely they will be sensitive to adjuvant endocrine therapies. For patients with ER-negative breast cancer, the recurrence risk is higher within the first 5 years after treatment and becomes negligible after 10 years.

Human Epidermal Growth Factor Receptor 2

HER2 is a transmembrane protein that is overexpressed in approximately 20% of breast cancers. Historically, HER2-positive tumors were associated with a higher risk of recurrence and an overall worse prognosis; however, the addition of therapies targeting the HER2 pathway, when combined with adjuvant chemotherapy, have improved prognosis. HER2-positive breast cancer is associated with a significantly increased risk of recurrence within the central nervous system compared with HER2-negative disease.

Triple-Negative Breast Cancer

Cancer cells that are ER negative, PR negative, and negative for overexpression of HER2 are frequently referred to as **triple-negative breast cancer**. These cancers tend to be the most responsive to chemotherapy, yet they are associated with a poorer overall prognosis compared with hormone receptor–positive or HER2-positive disease.

> **Key Definition**
>
> **Triple-negative breast cancer:** *cancer cells that are estrogen receptor–negative, progesterone receptor–negative, and negative for overexpression of human epidermal growth factor receptor 2.*

Grade

Histologic tumor grading is a semiqualitative evaluation that reflects breast cancer differentiation from normal breast tissue. Tumor grade is classified as low (grade I), intermediate (grade II), or high (grade III). Higher tumor grade is associated with increasing proliferation or aggressiveness of the cancer. Grade can be useful in guiding adjuvant treatment decisions.

Molecular Profiling

Analysis of the tumor genome is another way that prognosis can be established and is the only means by which prognosis can be personalized on the basis of an individual patient's tumor characteristics. The 21-gene expression assay Oncotype DX (Genomic Health, Inc) and the 70-gene expression assay MammaPrint (Agendia Inc USA) are commercially available assays for patients with ER-positive, HER2-negative breast cancer. The Oncotype DX results stratify a patient's risk of distant (metastatic) recurrence as low, intermediate, or high. The MammaPrint result is reported as a good (low risk) or poor (high risk) prognosis gene signature. In addition to providing prognostic information, both assays can predict benefit, or lack of benefit, from adjuvant chemotherapy. Results can guide clinicians to individualize the selection of adjuvant treatment on the basis of a patient's tumor biology, taken together with the prognostic information provided by the tumor stage.

Staging

Prognosis, which is associated with stage, is improving for patients with breast cancer at any stage. The current 5-year overall survival for patients with breast cancer is 89.7%. Five-year survival by stage is 98.9% for local disease confined to the breast, 85.2% for regional disease confined to the breast and regional lymph nodes, and 27% for stage IV disease.

In 2018, the 8th edition of the American Joint Committee on Cancer staging for breast cancer was implemented. It includes traditional anatomic stage (tumor size and lymph node status) combined with prognostic staging information (tumor grade and ER, PR, and HER2 receptor expression, as well as 21-gene expression assay results). These biomarkers not only provide prognostic information but also predict adjuvant therapy benefit and can help guide treatment decisions. The inclusion of biomarkers represents a substantial change in breast cancer staging but facilitates better alignment of prognosis with anatomic staging and the underlying disease biology. Given the complexity of the updated staging system, it will not be included in detail here; however, the interested reader can refer to: CA Cancer J Clin. 2017 Mar;67(4):290-303.

Therapy

In addition to anatomic and prognostic staging information, each patient's comorbid conditions, life expectancy, and preferences must also be taken into account when formulating

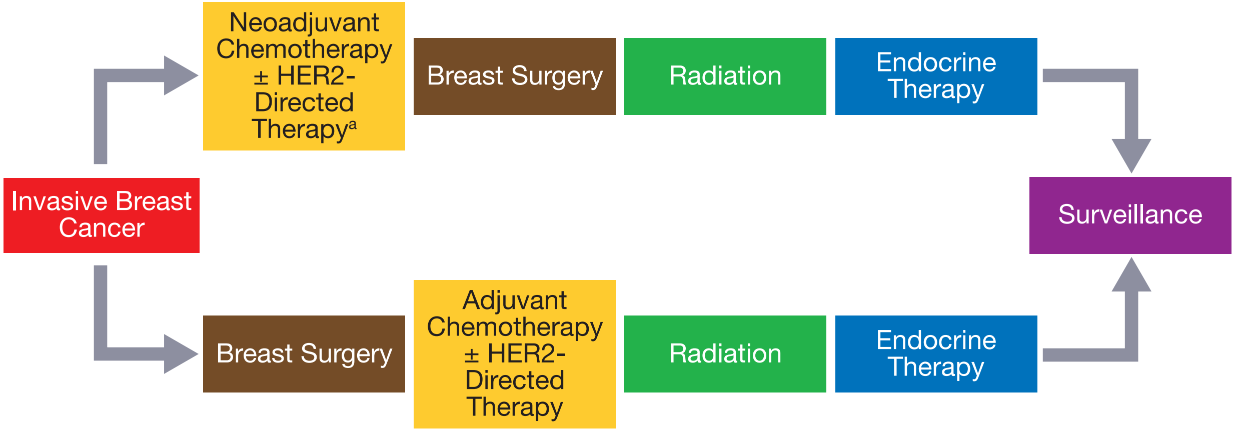

Figure 63.2. *Breast Cancer Treatment Overview.*
[a] Indications for neoadjuvant systemic therapy are to: 1) determine the responsiveness to systemic treatment by studying the tumor in vivo; 2) allow for a change in therapy for patients without response; 3) increase the chance for a breast-conserving operation; and 4) decrease the need for axillary lymph node dissection. HER2 indicates human epidermal growth factor receptor 2.

treatment decisions. Risks and benefits of each aspect of treatment (surgery, systemic therapy, and radiation therapy) must be individualized to each patient. Figure 63.2 provides a general algorithm for the treatment of breast cancer.

Ductal Carcinoma in Situ (Stage 0)

DCIS is primarily treated with local therapy—either mastectomy or lumpectomy (also known as breast-conservation surgery) with or without breast radiotherapy. For ER-positive DCIS, adjuvant endocrine therapy can be considered after lumpectomy. The selective ER modulator tamoxifen and the aromatase inhibitor anastrozole have both been shown to decrease the risk of a subsequent breast event (defined as either recurrent DCIS or the development of an invasive breast cancer in the ipsilateral or contralateral breast). Adjuvant endocrine therapy is not associated with an increase in survival, however, and it may confer risk of adverse effects.

Early-Stage Invasive Breast Cancer (Stages I-III)

Locoregional Therapy

Surgical resection of invasive breast cancer is achieved by either lumpectomy or mastectomy. Several randomized controlled trials that compared mastectomy with lumpectomy plus radiotherapy have demonstrated equivalent survival. Patients who elect to receive breast radiotherapy after lumpectomy have lower rates of recurrence in the ipsilateral breast compared with women who are treated by lumpectomy without radiotherapy. Those who undergo mastectomy have rates of ipsilateral breast cancer recurrence similar to those treated with lumpectomy plus radiotherapy.

Nearly all patients with invasive breast cancer should have sentinel lymph node surgery in conjunction with their definitive breast surgery. If a sentinel node is positive for metastasis, axillary lymph node dissection should be considered. Nomograms are available to predict the likelihood of additional lymph node involvement and to assess the need for node dissection. If the sentinel lymph node does not have metastatic tumor cells, the probability of other lymph nodes being affected is less than 5%. Compared with axillary lymph node dissection, sentinel lymph node surgery decreases late complications such as lymphedema. In a recent study of patients with clinical stage I breast cancer treated with lumpectomy and radiotherapy, long-term survival was equivalent for those with a positive sentinel lymph node who did and did not undergo axillary lymph node dissection.

Adjuvant Therapy

After surgical resection of breast cancer, the goal of systemic treatment (ie, adjuvant therapy) is to eliminate microscopic metastatic disease present at the time of diagnosis. Systemic treatment options may include chemotherapy, HER2-directed therapy, endocrine therapy, or various combinations for specific patients. Adjuvant therapy should generally be offered to patients with breast cancer with an intermediate or high risk of relapse, including most patients with lymph node–positive disease. Adjuvant therapy has been shown to decrease the risk of distant recurrence and improve overall survival regardless of patient age, tumor ER expression, or nodal status.

Chemotherapy can be of benefit to select patients regardless of the tumor's ER or HER2 status; however, triple-negative tumors tend to be the most responsive to chemotherapy. For patients with lymph node–negative disease, chemotherapy is typically advised for more biologically aggressive or proliferative tumors (more commonly triple-negative or HER2-positive disease). Chemotherapy is associated with more acute and long-term toxic effects than endocrine or HER2-directed therapy.

HER2-directed therapy only benefits patients with HER2-positive disease. Trastuzumab, a monoclonal antibody directed against HER2, is the most commonly used agent, although it has little activity as a single agent. When administered with chemotherapy, HER2-directed therapy has been associated with improved clinical outcomes compared with chemotherapy alone. Treatment is typically advised for patients with tumors larger than 1.0 cm regardless of nodal staging, and 1 year of trastuzumab remains the optimal duration of therapy.

Endocrine therapy is effective only for patients with ER-positive disease. It is typically offered to all patients with ER-positive disease and for many patients may be the only adjuvant therapy needed. Gene expression assays, such as Oncotype DX or MammaPrint, may help identify patients for whom chemotherapy may be omitted in lieu of endocrine therapy alone. Treatment typically lasts for 5 years with an option to extend it up to 10 years for select high-risk patients.

Neoadjuvant Therapy

The administration of systemic therapy before surgical resection (neoadjuvant therapy) is an increasingly common practice. Relapse rates and breast cancer survival are not affected by whether systemic therapy is administered before or after definitive breast surgery. Neoadjuvant systemic therapy was initially used for patients who were not surgical candidates, including those with inflammatory breast cancer. It was subsequently established for use in patients with large primary tumors desiring breast-conservation therapy. More recently, neoadjuvant systemic therapies have been evaluated in clinical trials studying the molecular, imaging, and clinical effects of therapy on breast cancer. Advantages of neoadjuvant therapy include being able to: 1) determine the responsiveness to systemic treatment by studying the tumor in vivo; 2) allow for a change in therapy for patients without a response; 3) increase the chance of a breast-conserving operation; and 4) decrease the need for axillary lymph node dissection. Patients with HER2-positive or triple-negative disease who achieve a pathologic complete response to neoadjuvant therapy (ie, no residual invasive cancer identified in the breast or axillary nodal specimens) at the time of operation have a more favorable overall prognosis than those who have residual disease. Neoadjuvant therapy can comprise chemotherapy, HER2-directed therapy, endocrine therapy, or a combination of these.

Metastatic (Stage IV) Disease

Approximately 5% to 10% of patients have stage IV disease at the time of initial diagnosis. The majority of occurrences of stage IV disease, however, represent systemic relapse several years or even decades after prior therapy for early-stage disease. Curative therapy for metastatic breast cancer is currently lacking. The median duration of survival with recurrent disease is 2.5 years, but the spectrum of survival is wide. In 2017, 5-year survival for stage IV disease was 27%. Survival is generally longer for patients with bone-only or soft-tissue disease than for patients with visceral metastases. It is also generally longer for patients with ER-positive or HER2-positive metastatic disease than for patients with triple-negative breast cancer.

Because treatment is not curative, the goals of treatment are to optimize quality of life and prolong life for as long as possible. The initial systemic treatment of ER-positive metastatic disease is usually endocrine therapy alone or in combination with an agent that targets one of the most common pathways of resistance to endocrine therapy. Chemotherapy is commonly reserved until resistance to endocrine therapy has occurred; however, it may be used as an initial or early line of therapy in patients with symptomatic disease or visceral crisis. An increasing number of HER2-directed therapeutic agents are available for patients with HER2-positive metastatic disease, but owing to limited single-agent activity, these agents are often administered in combination with another. More commonly, HER2-directed therapy is combined with endocrine therapy for patients with ER-positive disease or with chemotherapy regardless of tumor ER status. Chemotherapy is the only standard therapeutic option for triple-negative breast cancer. Combination chemotherapy increases tumor response rate, but it has not been shown to improve survival compared with sequential administration of single-agent chemotherapeutics. Combination chemotherapy should be reserved for patients who have symptomatic disease, rapid tumor progression, or imminent end-organ failure.

KEY FACTS

✓ LCIS—
  - a marker for increased risk of invasive carcinoma in either breast
  - not a precursor for invasive disease

✓ DCIS—a precancerous lesion that can develop into invasive cancer

✓ ER-positive breast cancer—generally portends a better prognosis than ER-negative breast cancer (given the same stage of disease)

✓ HER2-positive tumors—associated with a higher risk of recurrence and a worse prognosis

✓ DCIS therapy—
  - local therapy only (mastectomy or lumpectomy with or without radiotherapy)
  - if ER-positive, consider adjuvant tamoxifen after lumpectomy

✓ Surgical resection of invasive breast cancer—lumpectomy or mastectomy

✓ Metastatic (stage IV) breast cancer
  - most patients have had a relapse after treatment of early-stage disease, which may have occurred years or decades earlier (especially with ER-positive disease)
  - treatment is palliative

Therapeutic Agents

Chemotherapy

Many chemotherapeutic drugs are active against breast cancer. The anthracyclines (eg, doxorubicin and epirubicin) and the taxanes (eg, paclitaxel and docetaxel) are the most effective agents for breast cancer. Notably, a very small but real increased risk of secondary myelodysplastic syndrome and acute myeloid leukemia exists for patients receiving anthracycline-based chemotherapy. The anthracyclines are also associated with a dose-dependent increase in the risk of irreversible cardiomyopathy; thus, before therapy, all patients should undergo cardiac evaluation to assess baseline function. The taxanes may induce sensory peripheral neuropathy and neuropathic pain that is most commonly reversible with drug discontinuation. Platinum-based chemotherapy (eg, cisplatin or carboplatin) is associated with high tumor response rates in patients with germline *BRCA1* or *BRCA2* mutations and moderate response rates in patients with triple-negative breast cancer.

Endocrine Therapy

Tamoxifen is a selective ER modulator that is commonly used to treat both premenopausal and postmenopausal breast cancer. On some tissue (eg, breast), tamoxifen acts as an ER antagonist; whereas on other tissue (eg, bones, lipids, and uterus), it acts as an ER agonist. Its benefits include 1) antitumor effects on breast cancer cells, 2) decreased risk of contralateral breast cancer, 3) improved bone density in postmenopausal women, and 4) favorable effects on lipid profiles. Tamoxifen therapy also has adverse effects, including hot flashes, a 2- to 3-fold increased risk of venous thromboembolism, increased risk of endometrial cancer in postmenopausal women, and a slight increase in the risk of cataracts. Tamoxifen is metabolized into its active metabolites by the cytochrome P450 2D6 isozyme (CYP2D6); accordingly, patients who take medications that are strong CYP2D6 inhibitors (eg, paroxetine, cimetidine, and bupropion) should avoid these medications to eliminate drug-drug interactions that may decrease tamoxifen's efficacy.

Another class of endocrine agents, the **aromatase inhibitors** (including anastrozole, letrozole, and exemestane), can be used for the treatment of breast cancer in women who are postmenopausal by means of natural menopause, ovarian suppression (with a gonadotropin-releasing hormone agonist such as goserelin or leuprolide), or therapeutic bilateral salpingo-oophorectomy. The aromatase inhibitors block the peripheral conversion of androgens into estrogens. These drugs show a slight superiority to tamoxifen in reducing the risk of recurrence of breast cancer. They are not associated with an increased risk of thrombotic or endometrial events; however, they do increase the risk of osteoporosis and fractures, arthralgias, and vaginal dryness. These drugs are ineffective for premenopausal women who retain ovarian production of estrogen, and they are not advised for women who experience chemotherapy-induced amenorrhea unless used concurrently with ovarian suppression.

Many patients with ER-positive tumors will have primary (de novo) or secondary (acquired) resistance to endocrine therapies. New drugs known as CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) and mTOR inhibitors (everolimus) are now available to target pathways of endocrine resistance and resensitize tumors to endocrine therapies. These medications are orally administered, and each has certain adverse effects including neutropenia, rash, diarrhea, stomatitis, and substantial cost. These medications are currently only recommended for the management of metastatic disease; however, they are being evaluated in clinical trials as adjuvant therapy for high-risk early-stage disease.

Key Definition

Aromatase inhibitors: *hormonal agents that block peripheral conversion of androgens into estrogen and are used to treat breast cancer in postmenopausal women.*

HER2-Directed Therapy

Trastuzumab and pertuzumab are monoclonal antibodies directed against different domains of HER2 and have activity against HER2-positive breast cancers. As adjuvant therapy, trastuzumab, alone or in combination with pertuzumab for 1 year, is associated with a decrease in the risk of breast cancer recurrence and increased survival. In the metastatic setting, trastuzumab, pertuzumab, and taxane-based chemotherapy are preferred first-line treatment. Two additional HER2-directed therapies are approved for the treatment of HER2-positive metastatic breast cancer: lapatinib, an oral tyrosine kinase inhibitor of HER2, and ado-trastuzumab emtansine, a novel antibody-drug conjugate.

Bone-Modifying Therapy

The use of the bisphosphonates zoledronic acid and pamidronate can reduce the need for palliative radiotherapy, bone fixation, and pain medicine in patients with lytic bone metastases. A meta-analysis also supports the use of zoledronic acid or clodronate (at cancer doses) in postmenopausal patients who are candidates for adjuvant endocrine therapy. A 2- to 5-year intervention in this setting is associated with a decrease in the risk of bony metastatic relapse and improvement in both breast cancer–specific and overall survival. Furthermore, bisphosphonates are associated with improved bone mineral density and decreased risk of fractures in patients receiving antiestrogen therapy.

Denosumab is a monoclonal antibody directed against RANKL, which stimulates osteoclasts. This drug has been shown to decrease skeletal-related events in patients with bone metastases and in postmenopausal women receiving adjuvant endocrine therapy. As adjuvant therapy, long-term follow-up is still needed to determine the efficacy of denosumab in decreasing the risk of breast cancer relapse; thus, zoledronic acid is preferred in this setting. A major advantage of denosumab is its subcutaneous (as opposed to intravenous) administration and safety in patients with renal insufficiency; however, compared with the bisphosphonates, it is considerably more expensive and has a higher risk of hypocalcemia. Equivalent rates of osteonecrosis of the jaw (≈1%) have been observed in patients receiving bisphosphonates or denosumab.

Surveillance and Follow-up Care After Curative Therapy

After definitive therapy for breast cancer, patients are at risk for locoregional or systemic recurrence of the disease or for development of a new primary lesion. National guidelines for follow-up include obtaining history, review of systems, and physical examination every 3 to 6 months for the first 3 years after therapy, every 6 to 12 months for the fourth and fifth years, and annually thereafter. The only routine diagnostic testing indicated is annual mammography for patients who retain breast tissue.

In women with a prior history of breast cancer, use of breast MRI for surveillance is associated with high sensitivity and good specificity but high rates of false-positive results. There is no evidence that surveillance with MRI leads to improved survival, and as such, it is not justified for the vast majority of breast cancer survivors.

Intensive systemic laboratory surveillance (eg, tumor marker tests, liver function tests, and complete blood cell counts) and radiologic surveillance (eg, chest radiography, bone scan, computed tomography, and positron emission tomography) have not been shown to improve survival or other clinical outcomes, and they are not recommended for asymptomatic breast cancer survivors. Testing should be offered according to the development of new symptoms or suspicious physical examination findings.

Patients who have had breast cancer treatment should be followed up for late adverse effects of therapy. These include altered sexual function, mood disturbances, weight gain, and insomnia. Medical complications may include osteoporosis, peripheral neuropathy, myelodysplastic syndrome, and cardiac toxicity. Physical activity (30 minutes of moderate activity 5 times per week) and maintenance of a normal body mass index should be recommended because most studies have demonstrated their association with a decreased risk of cancer recurrence and improved overall survival.

Patterns of Recurrence

Long-term follow-up of women with ER-positive breast cancer is essential because the number of recurrences 5 to 15 years after diagnosis is the same as in the first 5 years after diagnosis. Patients with HER2-positive or triple-negative disease tend to have recurrences within the first 5 years after diagnosis. Relapse after 5 years for women with ER-negative breast cancer is uncommon.

Breast cancer tends to recur in bones, liver, lungs, or brain or locally in the chest wall or residual breast. Patients may have recurrences decades after the initial diagnosis, and this possibility must always be kept in mind if a patient has a history of ER-positive breast cancer. HER2-positive tumors have a higher chance of recurrence in the central nervous system.

KEY FACTS

✓ Benefits of adjuvant therapy—
- antitumor effects on breast cancer cells
- decreases risk of ipsilateral and contralateral breast cancer
- decreases risk of systemic relapse
- improves breast cancer–specific and overall survival

✓ Adverse effects of aromatase inhibitors—
- arthralgias
- vaginal dryness
- loss of bone mineral density
- increases risk of bone fractures

✓ Adverse effects of tamoxifen—
- hot flashes
- increases risk of thromboembolism (2- to 3-fold)
- increases risk of endometrial cancer in postmenopausal women
- slightly increases risk of cataracts

✓ Metabolism of tamoxifen—
- metabolized into its active metabolites by CYP2D6
- patients should not use tamoxifen with strong CYP2D6 inhibitors (eg, paroxetine, cimetidine, and bupropion)

✓ Benefits of bisphosphonates (eg, zoledronic acid and pamidronate) for lytic bone metastases—less need for palliative radiotherapy, bone fixation, and pain medicine

✓ Recommended surveillance after curative-intent therapy—history, physical examination, and, for those with residual breast tissue, annual mammography

✓ Follow-up that does *not* improve survival or outcomes and is *not* recommended after curative therapy—
- surveillance blood tests (tumor marker tests, liver function tests, and complete blood cell tests)
- other imaging studies (eg, chest radiography, bone scan, computed tomography, and positron emission tomography)

✓ Patients with history of ER-positive breast cancer may have recurrence decades after the initial diagnosis

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Cancer of Unknown Primary Origin and Paraneoplastic Syndromes

MICHELLE A. NEBEN WITTICH, MD

Carcinoma of Unknown Primary Origin

Carcinoma of unknown primary origin (CUP) describes a metastatic disease for which the primary cancer cannot be identified. Of all invasive cancers, 2% to 6% are CUP. The most common tumor associated with CUP is adenocarcinoma. Squamous cell carcinoma and undifferentiated neoplasms make up a smaller portion of CUP. When a pathologic diagnosis is established, additional evaluation should be tailored according to the patient's risk factors (eg, smoking and breast cancer risk), symptoms and signs, sites of metastasis, and the histologic diagnosis. Special consideration should be given to rule out possible curable malignant processes (eg, germ cell tumors or lymphoma) or treatable cancers (eg, breast, ovarian, or prostate cancer).

Key Definition

Carcinoma of unknown primary origin: *a metastatic disease for which the primary cancer cannot be identified.*

Patients with favorable subsets of CUP can have long-term survival with treatment tailored to their most likely disease. Women with axillary adenocarcinomas, with no clear breast primary lesion, should receive therapy for breast cancer. Women with peritoneal carcinomatosis generally undergo exploratory laparotomy with surgical cytoreduction, as they would for ovarian carcinoma. Men with bone metastases, particularly osteoblastic metastases, should have a prostate-specific antigen (PSA) test, and their tumor material should be stained for PSA expression.

Squamous cell carcinoma in isolated cervical lymph nodes should be treated as a locally advanced head and neck cancer, and squamous cell cancer in inguinal lymph nodes should be treated with surgery or radiotherapy (or both). Patients with poorly differentiated neuroendocrine carcinomas can respond well to systemic chemotherapy. Patients with a single small metastatic lesion can be treated with surgery or radiotherapy.

If a potentially treatable neoplasm is ruled out, most patients with CUP have a very poor prognosis, with an expected survival of 4 to 10 months. Some may benefit from palliative treatment (radiotherapy or chemotherapy); for many, the best options are supportive care and hospice care.

Paraneoplastic Syndromes

Paraneoplastic syndromes are caused by factors other than direct tumor invasion or compression. They do not necessarily indicate metastatic disease. Paraneoplastic syndromes can be classified as endocrine (Table 64.1), neurologic (Table 64.2), dermatologic (Table 64.3), or rheumatologic (Table 64.3).

Key Definition

Paraneoplastic syndrome: *the presence of symptoms due to factors other than direct tumor invasion or compression.*

Table 64.1 • Paraneoplastic Endocrine Syndromes

Syndrome	Clinical Presentation	Laboratory Findings	Associated Cancers
SIADH	Gait disturbances, falls, headache, nausea, fatigue, muscle cramps, anorexia, confusion, lethargy, seizures, respiratory depression, coma	Hyponatremia: mild, sodium 130-134 mmol/L; moderate, sodium 125-129 mmol/L; severe, sodium <125 mmol/L Increased urine osmolality (>100 mOsm/kg in the context of euvolemic hyponatremia)	SCLC, mesothelioma, bladder, ureteral, endometrial, prostate, oropharyngeal, thymoma, lymphoma, Ewing sarcoma, brain, GI, breast, adrenal
Hypercalcemia	Altered mental status, weakness, ataxia, lethargy, hypertonia, kidney failure, nausea and vomiting, hypertension, bradycardia	Hypercalcemia: mild, calcium 10.5-11.9 mg/dL; moderate, calcium 12.0-13.9 mg/dL; severe, calcium ≥14.0 mg/dL Low to normal (<20 pg/mL) PTH level Increased PTHrP level	Breast, multiple myeloma, renal cell, squamous cell (especially lung), lymphoma (including HTLV-associated lymphoma), ovarian, endometrial
Cushing syndrome	Muscle weakness, peripheral edema, hypertension, weight gain, centripetal fat distribution	Hypokalemia (usually potassium <3.0 mmol/L), increased baseline serum cortisol (>29.0 mcg/dL), normal to increased midnight serum ACTH (>100 pg/mL) not suppressed with dexamethasone	SCLC, bronchial carcinoid (neuroendocrine lung tumors account for ≈50%-60% of cases of paraneoplastic Cushing syndrome), thymoma, medullary thyroid cancer, GI, pancreatic, adrenal, ovarian
Hypoglycemia	Sweating, anxiety, tremors, palpitations, hunger, weakness, seizures, confusion, coma	For non–islet cell tumor hypoglycemia: low glucose, low insulin (often <1.44-3.60 mcIU/mL), low C-peptide (often <0.3 ng/mL), increased IGF-2:IGF-1 ratio (often >10:1) For insulinomas: low glucose, increased insulin, increased C-peptide, normal IGF-2:IGF-1 ratio	Mesothelioma, sarcomas, lung, GI

Abbreviations: ACTH, corticotropin; GI, gastrointestinal tract; HTLV, human T-lymphotropic virus; IGF, insulinlike growth factor; PTH, parathyroid hormone; PTHrP, parathyroid hormone–related protein; SCLC, small cell lung cancer; SIADH, syndrome of inappropriate antidiuretic hormone.

Modified from Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. Mayo Clin Proc. 2010 Sep;85(9):838-54. Erratum in: Mayo Clin Proc. 2011 Apr;86(4):364. Dosage error in article text; used with permission of Mayo Foundation for Medical Education and Research.

Table 64.2 • Paraneoplastic Neurologic Syndromes

Syndrome	Clinical Presentation	Associated Antibodies	Diagnostic Studies	Associated Cancers
Limbic encephalitis (LE)	Mood changes, hallucinations, memory loss, seizures, and, less commonly, hypothalamic symptoms (hyperthermia, somnolence, endocrine dysfunction); onset over days to months	Anti-Hu (typically with SCLC) Anti-Ma2 (typically testicular cancer) Anti-CRMP5 (anti-CV2) Antiamphiphysin	EEG: epileptic foci in temporal lobe(s); focal or generalized slow activity FDG-PET: increased metabolism in temporal lobe(s) MRI: hyperintensity in medial temporal lobe(s) CSF analysis: pleocytosis, increased protein, increased IgG, oligoclonal bands	SCLC (≈40%-50% of patients with LE), testicular germ cell (≈20% of patients with LE), breast (≈8% of patients with LE), thymoma, teratoma, Hodgkin lymphoma
Lambert-Eaton myasthenic syndrome (LEMS)	Lower-extremity proximal muscle weakness, fatigue, diaphragmatic weakness, bulbar symptoms (usually milder than in MG); later in course, autonomic symptoms (ptosis, impotence, dry mouth) in most patients	Anti–voltage-gated calcium channel (P/Q type)	EMG: low compound muscle action potential amplitude; decremental response with low-rate stimulation but incremental response with high-rate stimulation	SCLC (≈3% of patients have LEMS), prostate, cervical, lymphomas, adenocarcinomas
Myasthenia gravis (MG)	Fatigable weakness of voluntary muscles (ocular-bulbar and limb muscles), diaphragmatic weakness	Anti–acetylcholine receptor	EMG: decremental response to repetitive nerve stimulation	Thymoma (in ≈15% of patients with MG)

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalography; EMG, electromyography; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; Ig, immunoglobulin; MRI, magnetic resonance imaging; SCLC, small cell lung cancer.

Modified from Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. Mayo Clin Proc. 2010 Sep;85(9):838-54. Erratum in: Mayo Clin Proc. 2011 Apr;86(4):364. Dosage error in article text; used with permission of Mayo Foundation for Medical Education and Research.

Table 64.3 • Paraneoplastic Dermatologic and Rheumatologic Syndromes

Syndrome	Clinical Presentation	Diagnostic Studies and Laboratory Findings	Associated Cancers
Acanthosis nigricans	Velvety, hyperpigmented skin (usually on flexural regions); papillomatous changes involving mucous membranes and mucocutaneous junctions; rugose changes on palms and dorsal surface of large joints (eg, tripe palms)	Skin biopsy: histologic examination shows hyperkeratosis and papillomatosis	Adenocarcinoma of abdominal organs, especially gastric adenocarcinoma (≈90% of cancers in patients with acanthosis nigricans are abdominal); gynecologic
Dermatomyositis	Heliotrope rash (violaceous, edematous rash on upper eyelids); Gottron papules (scaly papules on skin overlying bony surfaces); erythematous rash (which may be photosensitive) on face, neck, chest, back, or shoulders (on shoulders, is known as *shawl sign*); proximal muscle weakness; swallowing difficulty; respiratory difficulty; muscle pain	Laboratory findings: increased serum CK, AST, ALT, LDH, and aldolase levels EMG: increased spontaneous activity with fibrillations, complex repetitive discharges, and positive sharp waves Muscle biopsy: perivascular or interfascicular septal inflammation and perifascicular atrophy	Ovarian, breast, prostate, lung, colorectal, non-Hodgkin lymphoma, nasopharyngeal
Erythroderma	Erythematous, exfoliating, diffuse rash (often pruritic)	Skin biopsy: histologic examination shows dense perivascular lymphocytic infiltrate	Chronic lymphocytic leukemia, cutaneous T-cell lymphoma (including mycosis fungoides), GI (colorectal, gastric, esophageal, gallbladder), adult T-cell leukemia or lymphoma, myeloproliferative disorders
Hypertrophic osteoarthropathy	Subperiosteal new bone formation on phalangeal shafts ("clubbing"), synovial effusions (mainly large joints), pain, swelling along affected bones and joints	Plain radiography: periosteal reaction along long bones Nuclear bone scan: intense and symmetric uptake in long bones	Intrathoracic tumors, metastases to lung, metastases to bone, nasopharyngeal carcinoma, rhabdomyosarcoma
Leukocytoclastic vasculitis	Ulceration, cyanosis, and pain over affected regions (especially digits); palpable purpura, often over lower extremities; renal impairment; peripheral neuropathy	Skin biopsy: histologic examination shows fibrinoid necrosis, endothelial swelling, leukocytoclasis, and erythrocyte extravasation	Leukemia or lymphoma, myelodysplastic syndromes, colon, lung, urologic, multiple myeloma, rhabdomyosarcoma
Paraneoplastic pemphigus (PNP)	Severe cutaneous blisters and erosions (predominantly on trunk, soles, and palms); severe mucosal erosions, including stomatitis	Serum antibodies to epithelia (against plakins and desmogleins) Skin biopsy: histologic examination shows keratinocyte necrosis,epidermal acantholysis, and IgG and complement deposition in epidermal and basement membrane zones	Non-Hodgkin lymphoma, chronic lymphocytic leukemia, thymoma, Castleman disease, follicular dendritic cell sarcoma
Polymyalgia rheumatica (PMR)	Limb girdle pain and stiffness	Laboratory findings: increased serum erythrocyte sedimentation rate (often not as high as in nonparaneoplastic PMR) and C-reactive protein	Leukemia or lymphoma, myelodysplastic syndromes, colon, lung, kidney, prostate, breast
Sweet syndrome (acute febrile neutrophilic dermatosis)	Acute onset of tender, erythematous nodules, papules, plaques, or pustules on extremities, face, or upper trunk; neutrophilia; fever; malaise	Skin biopsy: histologic examination shows a polymorphonuclear cell dermal infiltrate	Leukemia (especially acute myeloid leukemia), non-Hodgkin lymphoma, myelodysplastic syndromes, genitourinary tract, breast, GI, multiple myeloma, gynecologic, testicular, melanoma

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; EMG, electromyography; GI, gastrointestinal tract; Ig, immunoglobulin; LDH, lactate dehydrogenase.

Modified from Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. Mayo Clin Proc. 2010 Sep;85(9):838-54. Erratum in: Mayo Clin Proc. 2011 Apr;86(4):364. Dosage error in article text; used with permission of Mayo Foundation for Medical Education and Research.

Key Definition

Dermatomyositis: *a polymyositis with heliotrope rash (on the upper eyelids), Gottron papules (on bony surfaces), erythematous rash (on the face, neck, chest, back, or shoulders), proximal muscle weakness, swallowing difficulty, respiratory difficulty, and muscle pain.*

Key Definition

Sweet syndrome (acute febrile neutrophilic dermatosis): *a neutrophilic skin disease with an acute onset that is characterized by tender, erythematous nodules, papules, plaques, or pustules on the extremities, face, or upper trunk; neutrophilia; fever; and malaise.*

KEY FACTS

✓ CUP—2%-6% of all invasive cancers

✓ Syndrome of inappropriate antidiuretic hormone (SIADH)—
- gait disturbances, muscle cramps, falls
- headache, nausea, anorexia
- lethargy, fatigue
- confusion, seizures, respiratory depression, coma
- hyponatremia
- increased urine osmolality

✓ SIADH-associated cancers—
- small cell lung cancer, mesothelioma
- bladder, ureteral, endometrial, prostate
- oropharyngeal, gastrointestinal tract
- thymoma, adrenal
- Ewing sarcoma
- brain, breast

✓ Lambert-Eaton myasthenic syndrome (LEMS)—
- proximal muscle weakness of lower extremities
- fatigue
- diaphragmatic weakness
- bulbar symptoms (milder than in myasthenia gravis)
- later, autonomic symptoms (ptosis, impotence, dry mouth)

✓ LEMS-associated cancers—
- small cell lung cancer
- prostate, cervical
- lymphomas, adenocarcinomas

✓ Myasthenia gravis—
- fatigable weakness of voluntary muscles (especially ocular-bulbar and limb muscles), diaphragmatic weakness
- associated with thymoma in 15% of patients with myasthenia gravis

KEY FACTS

✓ Dermatomyositis-associated cancers—
- ovarian, breast, prostate
- lung
- colorectal
- non-Hodgkin lymphoma
- nasopharyngeal

✓ Polymyalgia rheumatica (PMR)—limb girdle pain and stiffness

✓ PMR-associated cancers—
- leukemia or lymphoma, myelodysplastic syndromes
- colon, lung, kidney
- prostate, breast

✓ Sweet syndrome–associated cancers—
- leukemia, non-Hodgkin lymphoma, myelodysplastic syndromes, multiple myeloma
- genitourinary tract, gynecologic, testicular
- breast
- gastrointestinal tract
- melanoma

65

Gynecologic Cancers: Cervical, Uterine, and Ovarian Cancers[a]

ANDREA E. WAHNER HENDRICKSON, MD

Cervical Cancer

Background

Globally, cervical cancer is the fourth most common type of cancer and the fourth leading cause of cancer death among women. The incidence varies geographically because of differences in the availability of screening programs and access to them. Approximately 85% of cervical cancer cases occur in less-developed regions of the world. For example, in Africa, cervical cancer is the leading cause of cancer deaths among women, but in the United States (US), where screening is more prevalent, cervical cancer is not among the top 10 causes of cancer deaths. In recent decades, the incidence of cervical cancer, along with the mortality rate associated with the disease, have markedly decreased. These changes have been attributed to widespread use of cytologic smear screening with the Papanicolaou (Pap) test and human papillomavirus (HPV) testing. Infection with HIV can promote progression of precancerous lesions, which contributes to a high volume of cervical cancer in regions with a higher prevalence of HIV, such as sub-Saharan Africa.

Risk Factors

Nearly all cervical cancer cases (99%) are associated with persistent HPV infection. Of the more than 100 types of HPV, only 13 subtypes have been definitively linked to cervical cancer. Persistent infection with one of the oncogenic HPV types—16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 (Table 65.1)—is the etiologic factor for development of the 2 most common types of cervical cancer: squamous cell carcinoma, which accounts for 75% of cases, and adenocarcinoma, which accounts for 20% to 24% of cases. HPV types 16 and 18 are the most common cancer-causing subtypes and account for 70% of the cervical cancers worldwide.

Accordingly, risk factors for cervical cancer include factors related to HPV exposure: first intercourse at an early age, more sexual partners, and a history of sexually transmitted infection. Smoking and chronic immunosuppression (such as in patients infected with HIV) increase the risk of persistent HPV infection and are therefore linked to cervical cancer pathogenesis.

Three vaccines against HPV have been approved by the US Food and Drug Administration for both sexes, to be administered at age 9 through 26 years. These are all prophylactic (not therapeutic) vaccines, created to prevent initial HPV infection. The bivalent vaccine (Cervarix; GlaxoSmithKline) protects against the 2 most common oncogenic strains (HPV types 16 and 18). The quadrivalent vaccine (GARDASIL; Merck & Co, Inc) targets HPV types 16 and 18, as well as 2 strains (HPV types 6 and 11) that are common causes of genital warts. The 9-valent vaccine (GARDASIL 9; Merck & Co, Inc) protects against HPV types 6, 11, 16, and 18 as well, but it also protects against HPV types 31, 33, 45, 52, and 58, which account for approximately 20% of cervical cancer cases. Since 2017, the 9-valent vaccine is the only vaccine available in the US; the availability of the individual vaccines varies by country.

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[a] Mayo Clinic does not endorse specific products or services included in this chapter.

Table 65.1 • Steps in Cervical Cancer Development

Step	Comments
1. Infection of the cervical epithelium with an oncogenic strain of HPV	HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 HPV types 16 and 18 are found in >70% of cervical cancers
2. Persistence of HPV infection	75%-80% of sexually active adults contract HPV Most infections are transient
3. Progression from persistent viral infection to precancerous lesion	Persistent infection can lead to development of high-grade cervical intraepithelial neoplasia
4. Development of a carcinoma	Cervical cancer develops in <1% of women infected with HPV

Abbreviation: HPV, human papillomavirus.

The dosing of GARDASIL 9 is based on age and timing of the vaccine schedule. For ages 9 through 14 years, a 2-dose regimen can be used, with the second dose given 6 to 12 months after the first dose. If the second dose is administered less than 5 months after the first dose, a third dose is required at least 4 months after the second dose. For ages 15 through 26 years, a 3-dose regimen is required, with the second dose 2 months after the first, and a third dose given 6 months after the first dose. Of note, even after a person has been vaccinated, cervical cancer screening is still required because the vaccine does not include all oncogenic strains of the virus. (See Chapter 36, "Preventive Medicine," for specific screening recommendations.)

Clinical Presentation

With most precursor lesions to cervical cancer, patients are asymptomatic. Patients with early cervical cancer can also be asymptomatic, or they may have abnormal vaginal bleeding, vaginal discharge, or dyspareunia. Patients with late-stage disease may have pelvic pain, leg pain, back pain, rectal bleeding, changes in bowel or bladder habits, and symptoms associated with local spread of the disease. Physical examination findings may include abnormal cervical epithelium that has a white discoloration after application of acetic acid (Figure 65.1); friable tissue, induration, or an exophytic mass on the cervix; or condylomata acuminata (Figure 65.2).

Prognosis

Patients with early-stage cervical cancer (stage IA—microscopic tumor) have a good prognosis, with a 5-year overall survival of approximately 93%. Patients with stage IV disease have a poor prognosis, with a 5-year overall survival of approximately 15%.

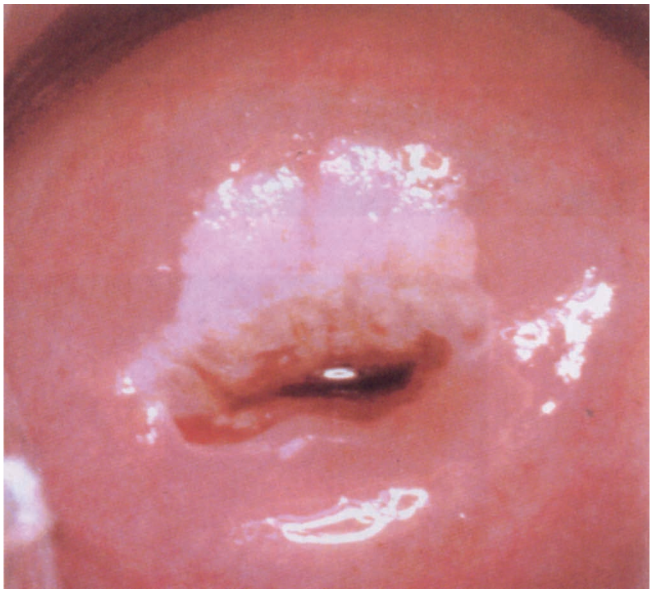

Figure 65.1. *Acetowhite Epithelium of the Anterior Lip of the Cervix. Cervical intraepithelial neoplasia, grade 2, was identified on biopsy.*

(From Massad LS. High-grade squamous intraepithelial lesions. In: Apgar BS, Brotzman GL, Spitzer M, editors. Colposcopy: principles and practice: an integrated textbook and atlas. 2nd ed. Philadelphia [PA]: Saunders/Elsevier; c2008; used with permission.)

Treatment

Treatment of a high-grade squamous intraepithelial lesion consists of removal of the affected area with a loop electrosurgical excision procedure (LEEP), cone biopsy, or cryosurgery. If other symptoms are present (eg, menorrhagia), hysterectomy can be performed. Treatment of invasive cervical cancer depends on the stage, which is determined clinically because of the limited availability of imaging worldwide. In early-stage disease, when the tumor is small (≤4 cm) and confined to the cervix, treatment includes a hysterectomy and possible radiotherapy. For very small (<2 cm) early-stage tumors in women who desire fertility preservation, trachelectomy (removal of the cervix with preservation of the uterus, including the lower uterine segment) with lymphadenectomy can be considered. If the tumor is larger (>4 cm) or involves the surrounding tissues, treatment consists of concurrent chemotherapy (usually weekly cisplatin) and pelvic radiotherapy followed by brachytherapy (intracavitary radiation). For distant metastases, the mainstay of therapy is chemotherapy (typically cisplatin and paclitaxel given in combination with bevacizumab, an antiangiogenesis agent) with localized radiotherapy used only if needed for symptom control.

KEY FACTS

- ✓ Most common types of cervical cancer—squamous cell carcinoma (75% of cases) and adenocarcinoma (20%-24% of cases)
- ✓ Cause of most cervical cancer—persistent infection with HPV types 16 and 18
- ✓ Treatment of cervical cancer—
  - surgery for small tumors
  - chemotherapy and radiotherapy for large tumors
  - removal of affected area with LEEP, cone biopsy, or cryosurgery for high-grade squamous intraepithelial lesion
  - varies for invasive cancer (according to the clinically determined stage)
- ✓ Prevention of cervical cancer—
  - bivalent, quadrivalent, and 9-valent vaccines
  - cervical cancer screening is still required for women who have received the vaccine

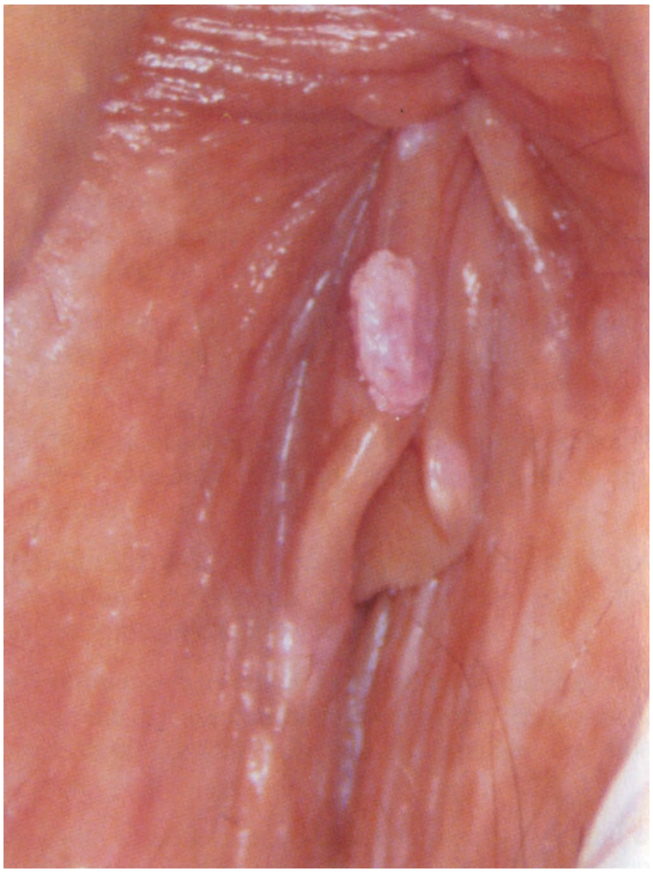

Figure 65.2. *Condyloma of the Labia Minora.*

(From Atlas of external genital condyloma. In: Apgar BS, Brotzman GL, Spitzer M, editors. Colposcopy: principles and practice: an integrated textbook and atlas. Philadelphia [PA]: W. B. Saunders Company; c2002. p. 380-82; used with permission.)

Uterine Cancer

Background

Uterine cancers are the most common type of gynecologic cancer in developed countries. Most of these tumors arise from the endometrium, with endometrioid adenocarcinoma accounting for 90% of endometrial cancers. Overall, endometrial cancer carries a more favorable prognosis than other types of cancer because symptoms often arise early. Thus, despite it being the most prevalent type of gynecologic cancer in the US, it is not among the top 5 causes of cancer death among US women.

Risk Factors

The majority of endometrial cancers (ie, type I or endometrioid subtype) are thought to be partly due to estrogen excess (long-term, unopposed estrogen exposure). Risk factors for endometrial cancer are listed in Box 65.1. The less common histologic subtypes of endometrial cancer, termed type II endometrial cancers, carry a less favorable prognosis and do not seem to depend on estrogen exposure (Table 65.2).

Approximately 10% of patients with endometrial cancer have a genetic predisposition to it. Women with hereditary nonpolyposis colorectal cancer (HNPCC; also known as Lynch syndrome) have a 30% to 60% lifetime risk of endometrial cancer (Table 65.3), and this accounts for approximately 3% to 5% of all endometrial cancers. Although women with HNPCC are at higher risk for endometrial cancer, the role of screening in this patient population is still uncertain. The risks and benefits of screening should be discussed with each woman. If a woman chooses to participate in screening, the preferred screening is annual endometrial biopsy starting at age 30 to 35 years or at 5 to 10 years before the earliest age at diagnosis of an HNPCC-related cancer in the woman's family.

Box 65.1 • Risk Factors for Endometrial Cancer

Unopposed estrogen
Tamoxifen therapy
Obesity
Diabetes mellitus
Advanced age
Polycystic ovary syndrome
Nulliparity
Late menopause

Table 65.2 • Classification of Endometrial Cancer

Type	Histologic Findings	Comment
I	Grades 1 and 2 endometrioid	Represents 80% of all endometrial cancers Preceded by an intraepithelial precursor lesion (atypical or complex endometrial hyperplasia) Better prognosis than with type II
II	Grade 3 endometrioid *or* Clear cell, mucinous, squamous, transitional, or undifferentiated	Not clearly associated with estrogen stimulation Often no precursor lesion Higher grade and worse prognosis than with type I

Clinical Presentation

The most common presenting symptom in women with endometrial cancer is abnormal uterine bleeding. The average age of women who have endometrial cancer is 61 years, so the uterine bleeding most associated with endometrial cancer is postmenopausal. However, abnormal uterine bleeding in women older than 35 years who have atypical glandular cells on a Pap test should be investigated with endometrial biopsy to rule out endometrial cancer. Pelvic ultrasonography most often shows a thickened endometrial stripe. Although most cases of postmenopausal bleeding are not endometrial cancer, this must be ruled out. As noted in Box 65.1, tamoxifen therapy has been associated with an increased risk of endometrial cancer. Therefore, postmenopausal women receiving tamoxifen therapy should have an annual gynecologic examination, and they should be monitored and counseled about symptoms of endometrial hyperplasia or cancer. Any abnormal vaginal or uterine symptoms in these patients should be addressed quickly. Pelvic ultrasonography and endometrial biopsies are recommended. An endometrial biopsy is required if the endometrial thickening is more than 4 mm, if there is increased echogenicity or inadequate visualization of the endometrium, or if bleeding persists.

Table 65.3 • Main Genetic Syndromes and Endometrial Cancer Risk

Syndrome	Associated Cancers	Lifetime Risk of Endometrial Cancer, %
Hereditary nonpolyposis colorectal cancer (Lynch syndrome)	Colorectal and endometrial (also ovarian, gastrointestinal tract, pancreas, hepatobiliary, urologic, and sebaceous)	40-60
Cowden syndrome	Most commonly breast, thyroid, and endometrial	13-19

Prognosis

Patients who have type I endometrial cancers usually have abnormal uterine bleeding early in the course of the disease, so those tumors are most often detected early, and the 5-year survival rate for stage I disease is 80% to 90%. Stage IV disease portends a poor prognosis, with 5-year survival rates between 20% and 30%.

Treatment

Surgery is the mainstay of treatment of early-stage disease. With early detection, a total hysterectomy is the treatment of choice, and no adjuvant therapy is required for type I endometrial cancers. In more advanced cases, as well as with the more aggressive type II endometrial cancers, the addition of radiotherapy or chemotherapy (or both) is considered, depending on factors such as tumor grade, size, depth of invasion, and involvement of the lower uterine segment. In recurrent cases, type I tumors can often be treated with endocrine therapy (eg, megestrol acetate).

KEY FACTS

✓ Uterine cancer—most (90%) are endometrioid adenocarcinoma (ie, type I endometrial cancer)

✓ Endometrial cancer—

- most are linked to estrogen excess
- most common presenting symptom is postmenopausal bleeding (but most cases of postmenopausal bleeding are not from endometrial cancer)
- pelvic ultrasonography shows thickened endometrial stripe

✓ Uterine bleeding in a patient receiving tamoxifen must be evaluated

Epithelial Ovarian Cancer

Background

Epithelial ovarian cancer (EOC) is the most lethal of the gynecologic cancers and is the fifth leading cause of cancer deaths among US women. EOC does not include germ cell tumors or stromal tumors, which are rare. Primary peritoneal and fallopian tube cancers are pathologically similar to EOC and have the same risk factors, interventions, and prognosis. This group of cancers develops primarily in older women (average age at onset, ≈60 years). It can occur in younger women, but those cases are most likely hereditary.

Risk Factors

Several risk factors are associated with the development of EOC (Box 65.2). In general, conditions that lead to an increased number of ovulatory cycles are thought to increase the risk of EOC; conversely, factors that decrease the number of ovulatory cycles are thought to decrease the risk of EOC. Use of oral contraceptives for more than 5 years can decrease the risk by approximately 50% (30%-60% depending on duration of use). Currently, no screening tests are recommended because no available test (including cancer antigen 125 [CA 125]) has sufficient specificity, sensitivity, or cost-effectiveness to be recommended for the general population. Approximately 85% of EOCs express CA 125, which is released into the circulation. However, it is detectable in only 50% of patients with stage I disease. The highest serum levels of CA 125 are found in patients with EOC, but the serum CA 125 level may be increased in other cancers and with pregnancy, endometriosis, and menstruation.

The risk of EOC increases if EOC develops in even 1 first-degree relative at any age. Additionally, several genetic syndromes increase the risk of EOC, which accounts for approximately 10% of cases of EOC (Table 65.4).

In women who are at high risk for EOC because of genetic predisposition (*BRCA1* or *BRCA2* mutation carriers), the National Institutes of Health Consensus Conference panel of experts recommends pelvic examination, CA 125 measurement, and pelvic ultrasonography every 6 to 12 months, beginning at age 35 years or at an age 5 to 10 years before the first diagnosis in the family. There is no conclusive evidence that this screening affects survival.

Box 65.2 • Risk Factors Associated With Ovarian Cancer

- Increased risk
  - Early menarche
  - Infertility
  - Nulliparity
  - Late menarche
  - Family history
  - *BRCA1*/*BRCA2* mutation
  - Hereditary nonpolyposis colorectal cancer
  - Endometriosis (certain types of ovarian cancer—clear cell, endometrioid, or low-grade serous carcinomas)
- Decreased risk
  - Oral contraceptive use
  - Pregnancy
  - Early pregnancy
  - Breastfeeding >1 y
  - Tubal ligation

In women with *BRCA1* or *BRCA2* mutations, prophylactic bilateral salpingo-oophorectomy is recommended at age 35 years or after completion of childbearing. Although the risk reduction (≈90%) is large, these women are still at risk for primary peritoneal carcinoma. The procedure also decreases the risk of breast cancer by approximately 50% in this high-risk population. (See Chapter 63, "Breast Cancer," for details about risk factors for breast cancer.)

Clinical Presentation

Although women may have symptoms secondary to EOC, these symptoms are often overlooked and nonspecific, and they often are not present until the tumor is quite large or has spread beyond the ovary or fallopian tube. Most women have gastrointestinal tract symptoms such as bloating, nausea, changes in bowel or bladder habits, and abdominopelvic pain, and approximately 75% of them receive a diagnosis of advanced disease (ie, the disease has spread beyond the pelvis). Occasionally, a patient has a pleural effusion (stage IV disease) at initial evaluation, and further work-up will identify ovarian or primary peritoneal cancer.

Prognosis

The prognosis for patients with EOC depends heavily on the stage at diagnosis (Table 65.5). If the disease can be detected at an early stage when the tumor has not spread beyond the inside of the ovary, overall survival is very good. Conversely, if the disease is diagnosed when it is advanced, overall 5-year survival is poor. Because of the lack of screening tests, about 75% of cases are detected in an advanced stage (stage III or IV), accounting for an overall 5-year survival for all stages of only 44%.

Treatment

The initial management of EOC includes thorough surgical staging and debulking, if possible. Outcome depends in part on the amount of tumor tissue remaining after the initial staging and debulking. Patients with no macroscopic residual disease after surgery fare better than those with any visible disease

Table 65.4 • Main Genetic Syndromes Related to Epithelial Ovarian Cancer

Syndrome	Genetic Changes	Lifetime Risk of Epithelial Ovarian Cancer[a], %
Hereditary breast and ovarian syndrome	*BRCA1* *BRCA2*	14-45 10-20
Hereditary nonpolyposis colorectal cancer (Lynch syndrome)	DNA mismatch repair (MMR) genes *MSH2*, *MLH1*, *MSH6*, *PMS1*, and *PMS2*	3-14

[a] Lifetime risk of epithelial ovarian cancer for women in the general population is 1.5%.

Table 65.5 • Epithelial Ovarian Cancer Prognosis by Stage

Stage	General Description	5-Year Survival, %
I	Tumor confined to the ovaries	>90 (grade 1; tumor not on surface of ovary) 75-80 (grade 3; clear cell histologic type; tumor on surface of ovary)
II	Tumor extends into the pelvis	60-70
III	Disease outside the pelvis (peritoneal metastases)	25-40
IV	Distant metastases, including intraparenchymal liver metastases or disease above the diaphragm	10-20

remaining. The goal is to achieve optimal surgical cytoreduction, which is defined as the patient having no remaining tumor nodule 1 cm or larger after surgery. This cytoreductive surgery should be performed by a gynecologic oncologist to achieve optimal debulking rates. Subsequently, patients receive chemotherapy based on platinum (cisplatin or carboplatin) and taxane (usually paclitaxel). The most common adverse effects of this drug combination include nausea, hair loss, fatigue, and cytopenias. Both of these agents can also cause substantial peripheral neuropathy.

If the disease is not amenable to surgical resection at the time of diagnosis, a few cycles of chemotherapy are given neoadjuvantly (chemotherapy given before surgery) in an attempt to decrease the tumor burden, decrease the surgical complexity, and increase the chances for an optimal cytoreductive procedure. After an interval debulking surgery, additional chemotherapy is given (as adjuvant chemotherapy).

If EOC is confined to the abdomen, intraperitoneal chemotherapy is effective. However, it is more difficult to tolerate and has a higher complication rate. Therefore, it is considered only in a subset of women who are otherwise healthy, have a good performance status, and have minimal to no residual disease after the initial surgical procedure.

In most patients, the tumors respond to the initial therapy, but in the majority of those patients, the tumor recurs. If it recurs within 6 months after the initial chemotherapy, the cancer is termed **platinum resistant** and, in general, single-agent chemotherapy is used, with a response rate of only 15% to 25% to any additional therapy. If the tumor does not recur within 6 months, the tumor is deemed **platinum sensitive**, and at the time of recurrence, a platinum doublet is again used. Platinum-sensitive tumors tend to have better responses to chemotherapy than platinum-resistant disease. Regardless of the type of recurrence, if the tumor has recurred, the treatment is generally considered palliative and not curative.

KEY FACTS

✓ Ovarian cancer—

- no screening tests are available for the general population
- mortality rate is high because most cases are detected at an advanced stage

✓ Treatment of EOC—

- thorough surgical staging and debulking
- most patients also need chemotherapy (unless EOC is confined to the inside of the ovary) with platinum-taxane doublet

✓ Recommendation for women with *BRCA1* or *BRCA2* mutations—prophylactic bilateral salpingo-oophorectomy at age 35 years, or after completion of childbearing

Key Definitions

Platinum resistant: *descriptor for ovarian cancer that recurs within 6 months after completion of initial chemotherapy.*

Platinum sensitive: *descriptor for ovarian cancer that does not recur within 6 months after completion of initial chemotherapy.*

66

Colorectal Cancer

JOLEEN M. HUBBARD, MD

Background

Colorectal cancer is diagnosed in approximately 137,000 Americans annually and causes 50,000 deaths each year. It is the third most common cause of cancer death in North America and Europe. The incidence of colorectal cancer has decreased since the early 2000s, after it peaked in the late 1990s. The decrease in colon cancer incidence and mortality rate is attributed to improved screening methods, consisting mainly of endoscopic surveillance. Screening colonoscopy should be initiated by age 50 years for persons with average risk. Screening may be initiated at a younger age for high-risk patients, such as those with a family history of colorectal cancer, an inherited familial colon cancer syndrome, or inflammatory bowel disease.

Risk Factors

Approximately 10% of colorectal cancer is related to familial syndromes that have been defined or are still undefined. High-risk groups include the following: 1) persons with familial polyposis syndromes (ie, familial adenomatous polyposis [for which a gene has been identified on chromosome 5] and **Gardner syndrome** [gut polyps in combination with desmoid tumors, lipomas, sebaceous cysts, and other abnormalities]), accounting for 1% of colorectal cancers; 2) persons with familial cancer syndromes without polyps (ie, **hereditary nonpolyposis colorectal cancer** [also called **Lynch syndrome**], which is marked by colon cancer with or without endometrial, breast, and other cancers), accounting for 3% to 4% of colorectal cancers; and 3) persons with inflammatory bowel disease (incidence of colorectal cancer, 12% after 25 years).

Key Definition

Gardner syndrome: *a familial polyposis syndrome with gut polyps in combination with desmoid tumors, lipomas, sebaceous cysts, and other abnormalities.*

Key Definition

Hereditary nonpolyposis colorectal cancer (Lynch syndrome): *a familial cancer syndrome without polyps that is marked by colon cancer with or without endometrial, breast, and other cancers.*

Most cases of colorectal cancer are sporadic, lacking the aforementioned risk factors. Diet and lifestyle are becoming increasingly recognized as risk factors for colorectal cancer. High-fat and low-fiber diets, decreased levels of physical activity, and obesity are all associated with an increased risk of colorectal cancer.

Treatment

Surgery

For treatment with curative intent, surgical resection is preferred for carcinomas of the colon or rectum. Surgical exploration and resection allow for pathologic determination of tumor depth of penetration through the bowel wall and assessment of regional lymph nodes. Prognosis is directly related to the stage of disease (Table 66.1). Five-year survival rates for locoregional disease have improved in recent decades as a result of many factors, including improvements in preoperative staging,

Table 66.1 • Staging of Colorectal Cancer and Survival

AJCC Stage	Depth of Penetration	Lymph Node Status	5-Year Survival, %
I	Submucosa or muscularis	Negative	97
II	Through muscularis or to other organs	Negative	
IIA			86
IIB			80
IIC			58
III	Any	Positive	
IIA			79-90
IIB			53-74
IIC			15-40

Abbreviation: AJCC, American Joint Committee on Cancer.

Data from Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A 3rd, editors. AJCC Cancer Staging Manual. 7th ed. New York (NY): Springer; c2010. p. 148.

surgical technique, and adequate lymph node retrieval, and the use of neoadjuvant (preoperative) and adjuvant (postoperative) therapy.

Adjuvant Therapy

The recommendation for node-positive (stage III) colon cancer is to administer adjuvant chemotherapy with a multidrug regimen that includes oxaliplatin and a fluoropyrimidine (5-fluorouracil or capecitabine). Controversy exists about standard recommendations for deeply invasive but lymph-node negative (stage II) colon carcinomas. Adjuvant chemotherapy is recommended for patients who have high-risk stage II disease and any of the following characteristics: perforation or obstruction, tumor penetrating the visceral peritoneum or adherent to other structures, or fewer than 10 lymph nodes identified in the surgical specimen. For rectal cancer, a combination of fluoropyrimidine-based chemotherapy and pelvic radiotherapy, preferably administered preoperatively (as neoadjuvant therapy), is standard for stage II and III disease. Postoperative chemotherapy includes combination fluoropyrimidine and oxaliplatin for high-risk stage II and stage III disease.

Approach to Metastatic Disease

Certain patients with oligometastatic colorectal cancer in the lung or liver (or both) may be candidates for an attempt at curative resection of the metastatic disease. Of carefully selected patients with minimal metastatic disease, 30% to 40% survive beyond 5 years (many without further evidence of disease recurrence) after resection of metastatic lesions and systemic chemotherapy.

Palliative chemotherapy is the only option for most patients with advanced metastatic colorectal cancer. The median duration of survival is ≈30 months when patients are given medical therapy and are exposed to all active treatments of this disease.

Doublet cytotoxic chemotherapy regimens (a fluoropyrimidine in combination with oxaliplatin or irinotecan) administered with a biologic agent (bevacizumab, cetuximab, or panitumumab) are the standard of care for first- and second-line treatment of metastatic colorectal cancer. Like other platinum agents, oxaliplatin can cause chronic peripheral neuropathy, and oxaliplatin has the unique adverse effect of acute sensory neuropathy for cold, which resolves several days after completion of treatment. Irinotecan (a topoisomerase inhibitor) and the fluoropyrimidines are associated with adverse effects that include mucositis, diarrhea, nausea, vomiting, palmar-plantar dysesthesia, and cytopenias.

Bevacizumab is a monoclonal antibody targeting the vascular endothelial growth factor ligand and improves survival when combined with cytotoxic chemotherapy. Common adverse effects of bevacizumab include hypertension, epistaxis, proteinuria, and a rare incidence of thrombosis. Bevacizumab should not be administered within 8 weeks before a surgical procedure because of the risk of delayed wound healing and gastrointestinal tract perforation.

Cetuximab and panitumumab are monoclonal antibodies that target the endothelial growth factor receptor (EGFR) and improve survival outcomes when used alone or in combination with cytotoxic chemotherapy. These EGFR inhibitors cause the characteristic adverse effect of an acneiform rash that may be ameliorated with tetracycline and corticosteroid creams. Patients who have tumors with a mutation involving Ras, a protein in the signal-transduction cascade downstream from EGFR, are not eligible for treatment with either of the EGFR inhibitors.

If patients have disease progression or intolerance of the aforementioned treatments, several additional options are approved for the treatment of metastatic colorectal cancer.

Regorafenib is an oral multikinase inhibitor that targets angiogenesis and mechanisms of resistance to antiangiogenic therapy. Common adverse effects of regorafenib include diarrhea, palmar-plantar erythrodysesthesia, hypertension, and fatigue.

Trifluridine/tipiracil is a thymidine analogue that leads to DNA dysfunction when incorporated into cancer cells. The main adverse effects of trifluridine/tipiracil are hematologic (neutropenia, anemia, and thrombocytopenia), as well as mild nausea, vomiting, and fatigue.

The *immune checkpoint inhibitors* are approved for use in the 5% of patients with metastatic colorectal cancer with microsatellite instability. Pembrolizumab and nivolumab are both monoclonal antibodies targeting the programmed cell death 1 (PD-1) receptor, a mechanism that some cancer cells use to evade the immune system. Among heavily pretreated patients, pembrolizumab and nivolumab have led to response rates of 26% and 27%, as well as disease control rates of 50% and 62%, respectively. The robust and sustained responses of anti-PD-1 antibodies have made them the most exciting recent advancement in the treatment of metastatic colorectal cancer. Ongoing studies are investigating their use in earlier lines of therapy either as monotherapy or in combination with standard first-line therapy.

Surveillance After Curative Resection

Current American Society of Clinical Oncology guidelines recommend that the carcinoembryonic antigen (CEA) level be checked preoperatively. After curative-intent treatment of colon cancer in patients with stage II or III disease, the guidelines recommend that the CEA level be checked every 3 to 6 months for 2 years and then every 6 months for a total of 5 years if the patient's general medical condition would allow the patient to be a candidate for surgical intervention or chemotherapy. Monitoring of CEA may also be useful for determining the response of metastatic disease to therapy.

Computed tomography of the abdomen and pelvis, as well as chest imaging, should be performed every 6 to 12 months for the first 3 years after diagnosis and then yearly through the fifth year. Patients must receive adequate endoscopic surveillance for colon cancer recurrence. This surveillance should be performed at 1 and 4 years after surgery and every 5 years thereafter. If a patient's entire colon could not be endoscopically visualized before surgery, colonoscopy should be performed within 6 months after surgery to assess for a synchronous colon cancer.

KEY FACTS

✓ Screening colonoscopy—begin at age 50 years for persons at average risk for colorectal cancer

✓ Surgical resection—curative treatment of carcinomas of the colon or rectum

✓ Adjuvant chemotherapy—

- recommended for node-positive (stage III) colon cancer
- multidrug regimen (oxaliplatin and either 5-fluorouracil or capecitabine) for 6 months

✓ Oligometastatic colorectal cancer in the lung or liver (or both)—certain patients may be candidates for an attempt at curative resection of metastases

✓ CEA levels for surveillance—

- check CEA preoperatively
- check CEA every 3-6 months for the first 2 years after curative treatment of colon cancer
- then check CEA every 6 months for a total of 5 years (if patient is still a candidate for surgical intervention or chemotherapy)

✓ Imaging for surveillance for colon cancer recurrence—

- computed tomography of the abdomen and pelvis *and* chest imaging every 6-12 months for 3 years after diagnosis and then yearly through the fifth year
- colonoscopy at 1 and 4 years after surgery and then every 5 years

67 Genitourinary Cancer

BRIAN A. COSTELLO, MD

Prostate Cancer

Background

Approximately 165,000 new cases of prostate cancer occur annually in the United States (US). It is the most common cancer in men in the US and is the second leading cause of cancer death in US men (29,000 deaths annually). Risk factors for prostate cancer include older age, race (African American), family history (first-degree relative), and possibly dietary fat intake. The lifetime probability of prostate cancer developing in a man is 1 in 6.

Prostate-Specific Antigen

The use of prostate-specific antigen (PSA) for prostate cancer screening is controversial. In fact, the number of new cases of prostate cancer diagnosed in the US has decreased substantially in the past several years as screening guidelines have changed. PSA is produced by normal and neoplastic prostatic ductal epithelium. Its concentration is proportional to the total prostatic mass. The inability to distinguish benign prostatic hyperplasia from carcinoma on the basis of the PSA level renders it inadequate as the sole screening method for prostate cancer. However, PSA is useful for monitoring response to therapy in cases of known prostate cancer, particularly after radical prostatectomy, when PSA should be undetectable.

Prognostic factors for prostate cancer include stage of disease, grade of tumor, and pretreatment PSA level. The Gleason scoring system is used for pathologic grading of tumors. The surgical specimen is graded by adding the grade (1-5) of the predominant pattern of differentiation to the grade (1-5) of the secondary architectural pattern (eg, 4+5=9). Gleason grades 2 through 6 are associated with a better prognosis than Gleason grades of 8 or more. Many pathologists believe, however, that the lowest grade for any single pattern is 3, which makes the lowest total Gleason grade seen in clinical practice a 6 (3+3). Retrospective results indicate that the pretreatment PSA value is a strong predictor of disease outcome after surgery or radiotherapy.

Management

Management of Specific Stages

Prostate cancer is a disease of older men, so comorbid conditions, patient age, and performance status must be considered when selecting a therapy because more men will die *with* prostate cancer than *of* prostate cancer. In general, patients with Gleason grade 6 tumors are observed without treatment. For organ-confined prostate cancer, radiotherapy and radical prostatectomy are equally viable options. For locally advanced tumors, radiotherapy is generally used. For disease with positive pelvic nodes, the management is varied. Divergent approaches include androgen deprivation alone, radiotherapy with or without androgen deprivation, close observation with androgen deprivation at progression, or prostatectomy with or without androgen deprivation.

Prostatectomy

Prostatectomy is reserved for patients with localized disease. The 15-year disease-specific survival rate after prostatectomy is 85% to 90% among these patients. Nerve-sparing prostatectomy preserves sexual potency in 68% to 86% of patients. Risk of impotence increases with increasing age, size of tumor, extent of spread, and preoperative sexual function. Total urinary incontinence is rare (<2% of patients), although many men have some degree of incontinence after prostatectomy.

Radiotherapy

External beam radiotherapy is considered the equivalent of prostatectomy for overall survival. Impotence occurs less often than with prostatectomy. Chronic radiation proctitis is not uncommon.

Patients with organ-confined prostate cancer may also be candidates for **brachytherapy**. In this procedure, hundreds of radioactive seeds are placed in the prostate gland through a transrectal approach. This treatment works as well as external beam radiotherapy in appropriately selected patients and is less likely to cause radiation proctitis or impotence, but brachytherapy is less likely to adequately treat patients with extraprostatic spread of disease. Brachytherapy also requires fewer treatments and thus is often attractive to patients who live a long distance from the radiotherapy center.

Key Definition

Brachytherapy: *radiotherapy with the radiation source located near the target; for prostate cancer, many radioactive seeds are placed in the prostate gland through a transrectal approach.*

Androgen Deprivation Therapy

In patients with metastatic disease, bone is the most frequent site of metastatic disease. Although androgen deprivation therapy, also known as hormonal therapy, is effective and produces a response in most patients, it is noncurative. The average duration of response to initial hormonal therapy is 18 to 24 months. The average duration of survival is approximately 5 years after diagnosis of metastatic disease.

The sources of androgens in men are the testes (testosterone, 95%) and the adrenal glands (5%). Androgen deprivation therapy can be accomplished surgically (with orchiectomy) or medically. Potential agents include luteinizing hormone–releasing hormone (LHRH) agonists such as leuprolide, buserelin, and goserelin. They decrease androgen levels through continuous binding of the LHRH receptor and subsequent decrease of luteinizing hormone and thus testosterone. They are administered as a depot injection every 1 to 6 months, depending on dosing. An LHRH antagonist, degarelix, also can be used. Androgen deprivation therapy can be associated with adverse effects, including decreased libido, impotence, gynecomastia, osteoporosis, irritability, weight gain (and metabolic syndrome), and an increased risk of myocardial infarction.

Chemotherapy

Previously, prostate cancer was considered refractory to most chemotherapy regimens. Approved by the US Food and Drug Administration (FDA) in 2004, docetaxel in combination with prednisone has resulted in not only considerable responses but also improved survival among men with metastatic, hormone-refractory prostate cancer. More recently, docetaxel has been shown to improve survival for some men when given earlier after the finding of metastatic disease, in the so-called hormone-sensitive phase. Cabazitaxel has been FDA approved for use after docetaxel.

Prevention of Skeletal-Related Events

Development of painful and debilitating fractures is a common adverse effect in men with bone metastases from prostate cancer. Bisphosphonates and the more recently approved RANK ligand inhibitors, such as denosumab, reduce the risk of skeletal-related events. Thus far, these agents have been shown to be beneficial only in metastatic hormone-refractory adenocarcinoma of the prostate and not in the metastatic hormone-sensitive state. Although they reduce the morbidity of skeletal-related events, these agents do not improve overall survival.

Novel Therapies for Metastatic Hormone-Refractory Prostate Cancer

In recent years, several new-generation, FDA-approved medications have become available for use in men with metastatic hormone-refractory prostate cancer. Abiraterone is an androgen biosynthesis inhibitor that is given along with prednisone and administered orally once daily. Enzalutamide, an androgen receptor signaling inhibitor, similarly is given orally once daily, but use of prednisone with this agent is not required. Both drugs are approved for use before or after docetaxel chemotherapy. An autologous cellular immunotherapy, sipuleucel-T, is available for use in advanced prostate cancer and works by stimulating the patient's own immune system against the prostate cancer. The newest therapy is radium 223 dichloride, a nuclear medicine therapy (specifically, an alpha emitter) that targets bone metastases with alpha particles. This agent has been shown to benefit patients by increasing the time to first symptomatic skeletal event, improving quality of life, and increasing overall survival. This treatment, which is generally well tolerated, is given intravenously every 4 weeks for a total of 6 treatments.

Follow-up Recommendations

After curative therapy for prostate cancer (ie, prostatectomy or radiotherapy), the PSA level can be used as a marker for recurrence. PSA should be undetectable after successful primary surgical therapy, but some PSA will persist after radiotherapy. Generally, biochemical recurrence is indicated by an increasing PSA level compared with either a nondetectable level or the nadir after definitive local therapy. This increase indicates recurrent disease in a patient with no identifiable metastases on radiographic imaging such as bone scan, computed tomography (CT), or other novel imaging modalities. If prostate cancer recurs after definitive local therapy and the patient is not receiving ongoing therapy, the median time between identification of an increased PSA level (biochemical recurrence) and development of symptoms from metastatic prostate cancer can be several years in some instances. If metastatic disease is identified, survival is, on average, 5 to 6 years with available therapies. Thus, how closely a patient is monitored depends on his overall health, comorbid conditions, and overall life expectancy.

KEY FACTS

✓ PSA level—

- does not distinguish benign prostatic hyperplasia from carcinoma
- inadequate as sole screening method for prostate cancer
- useful after radical prostatectomy (PSA level should be undetectable)

✓ Considerations for prostate cancer therapy—

- comorbid conditions, patient age, and performance status
- more men die *with* prostate cancer than *of* prostate cancer

✓ Therapy for prostate cancer—

- prostatectomy for localized disease
- external beam radiotherapy (similar overall survival as with prostatectomy)
- brachytherapy for some organ-confined cases
- androgen deprivation therapy (hormonal therapy) is effective for metastatic disease but is noncurative
- chemotherapy produces responses and may improve survival

Testicular Cancer

Background

Testicular cancer is diagnosed in approximately 9,000 men annually. It is the most common solid cancer in males aged 15 to 35 years, and it is typically curable, even if metastatic. High-risk factors are cryptorchid testes (40-fold relative risk) and Klinefelter syndrome (these patients also have an increased risk of breast cancer). The 2 broad categories of testicular cancer are seminomas and nonseminomas. Types of nonseminomas include embryonal carcinoma, mature and immature teratoma, choriocarcinoma, yolk sac tumor, and endodermal sinus tumor. Often an admixture of several cell types occurs within nonseminomas. Any nonseminomatous component that is present with a seminoma is treated like a nonseminoma.

Evaluation includes 1) measurement of β-human chorionic gonadotropin (β-HCG), alpha fetoprotein (AFP), and lactate dehydrogenase levels and 2) CT of the abdomen (retroperitoneal lymph nodes) and chest (mediastinal lymph nodes or pulmonary nodules).

Staging

Unlike other cancers that have 4 stages, testicular cancer has only 3 stages. Stage I disease is confined to the testis, stage II includes infradiaphragmatic nodal metastases, and stage III is spread beyond retroperitoneal nodes. About 85% of nonseminomas are associated with an increased value of β-HCG or AFP. Approximately 15% to 20% of advanced seminomas are associated with an increased β-HCG level. The AFP value is never increased in pure seminoma; if it is increased, the tumor is nonseminoma and should be treated as such.

Management

Radical inguinal orchiectomy is the definitive procedure for both pathologic diagnosis and local control. Scrotal orchiectomy and biopsy should not be done, because they are associated with a high incidence of local recurrence or spread to inguinal nodes. Thus, a patient with a testicular mass should undergo ultrasonographic evaluation and be referred to a urologist.

Bladder Cancer

Background

Approximately 81,000 new cases of bladder cancer are diagnosed in the US each year, and approximately 17,000 people die each year of bladder cancer. The principal risk factor for bladder cancer is smoking, and 50% of cases of bladder cancer in the US are directly attributable to tobacco use. Active smokers have 4 times the risk of bladder cancer compared with the general population, and former smokers have 2 times the risk.

Other risk factors include occupational exposure to substances such as dyes, arsenic, and aromatic amines. Previous cyclophosphamide chemotherapy is also a risk factor. In certain developing countries, infection with *Schistosoma haematobium* is a risk factor that accounts for up to 50% of cases.

Staging

Histologically, more than 90% of bladder cancers are urothelial carcinomas (also known as transitional cell carcinoma), and a small percentage can be either squamous cell carcinoma or adenocarcinoma. Localized bladder cancers are generally categorized as either non–muscle invasive (superficial) or muscle invasive, in which the bladder tumor invades into or beyond the muscularis propria of the bladder wall. Bladder cancers may spread to the regional lymph nodes and also to more distant sites.

Management

Non–muscle-invasive bladder cancer is typically managed by urologists with periodic cystoscopy and resection of recurrent tumors as warranted. Furthermore, BCG (bacillus Calmette-Guerin) or chemotherapy can be instilled into the bladder to help prevent recurrence and progression to muscle-invasive disease. If muscle-invasive bladder cancer develops, more aggressive treatment is necessary. Typically, the 2 options are 1) neoadjuvant cisplatin-based chemotherapy with subsequent cystectomy and 2) trimodality therapy (cystoscopic resection of the bladder tumor with a subsequent combination of radiotherapy and chemotherapy). Even with aggressive therapy for muscle-invasive bladder cancer, patients have a high risk of recurrent metastatic disease. For patients with metastatic disease, the treatment is chemotherapy and, more recently, immunotherapy. (Generally, surgery and radiotherapy are not useful.) Chemotherapy is not curative, and the average survival of patients with metastatic bladder cancer is 12 to 16 months with treatment.

Kidney Cancer

Background

Each year in the US, 65,000 new cases of kidney cancer are diagnosed, most of which are localized to the kidney. Approximately 25% to 33% of kidney cancers are metastatic at presentation, and approximately 15,000 people die of kidney cancer annually. Half of all kidney cancers are discovered incidentally when patients are asymptomatic and having imaging tests for other reasons. Historically, renal cell carcinoma (RCC) was known as the internist's tumor, with the classic triad of flank pain, hematuria, and palpable abdominal mass, although now only 9% of patients have this triad at diagnosis.

The evaluation typically includes CT of the chest, abdomen, and pelvis. Under some circumstances, magnetic resonance imaging of the abdomen and pelvis may be used. Approximately 5% to 8% of patients with kidney cancer will have development of brain metastases. The initial work-up will sometimes include routine brain imaging with CT or magnetic resonance imaging—certainly in the setting of neurologic symptoms. Positron emission tomography is not an effective imaging modality for kidney cancer and has no role in the diagnosis, staging, or follow-up of RCC.

Staging

About 75% of RCCs are clear cell cancers. Others include papillary RCC, chromophobe RCC, and oncocytomas. Any of these subtypes can be associated with sarcomatoid features, which universally portend a poor prognosis. About 2% of RCCs are associated with inherited syndromes, most commonly von Hippel-Lindau syndrome.

Management

Localized kidney cancers (and some with regional lymph node involvement) are treated surgically. Radiotherapy is not used for the primary tumor. Some small renal masses found incidentally are observed and treated only if clinically warranted, either with surgery or with ablation, by an interventional radiologist. In contrast to other metastatic cancers, removal of the primary tumor in the kidney (**cytoreductive nephrectomy**) is considered even if a patient has stage IV disease, because some patients who undergo cytoreductive nephrectomy in combination with systemic therapy will live longer. If a kidney cancer is localized and treated with surgical removal, there is currently no evidence that adjuvant treatment will help decrease the risk of recurrence, although this question is under active investigation.

Key Definition

Cytoreductive nephrectomy: *removal of the primary tumor in the kidney.*

For patients who have metastatic disease, the main treatment is systemic therapy. Traditional chemotherapy generally is not used in the treatment of advanced kidney cancer. Since December 2005, the FDA has approved 10 drugs for the treatment of advanced kidney cancer. None are curative, but all of them slow the progression of the disease, and the average survival with medical therapy for metastatic RCC is 2 to 3 years. Most of these drugs are administered orally.

One category, the tyrosine kinase inhibitors, includes sorafenib, sunitinib, pazopanib, axitinib, and cabozantinib. All of these are administered orally. Each has its own adverse effect profile, but some important adverse effects of this class include hypertension, hypothyroidism, fatigue, increased liver function test results, diarrhea, and congestive heart failure. Another class is the mTOR inhibitors (oral everolimus and intravenous temsirolimus). Notable adverse effects with the mTOR inhibitors include hyperlipidemia (especially hypertriglyceridemia), hyperglycemia, diarrhea, and noninfectious pneumonitis. Another agent approved for use in RCC and other cancers is bevacizumab, which is an inhibitor that exclusively targets vascular endothelial growth factor and is administered intravenously. Important adverse effects include gastrointestinal tract perforation, which can occur in up to 2.4% of patients, and surgical wound healing complications. Bevacizumab should be discontinued at least 28 days before elective surgery and held at least 28 days after elective surgery and until the surgical wound is fully healed. Bevacizumab carries an increased risk of causing hemorrhage. Most recently, immunotherapy has been FDA approved for use in metastatic RCC.

Hematuria

Gross hematuria and microscopic hematuria can be presenting symptoms of genitourinary cancers, especially bladder and kidney cancer. All adult patients who report gross hematuria should undergo a urologic work-up, as well as those who have clinically confirmed, asymptomatic microscopic hematuria (Figure 67.1).

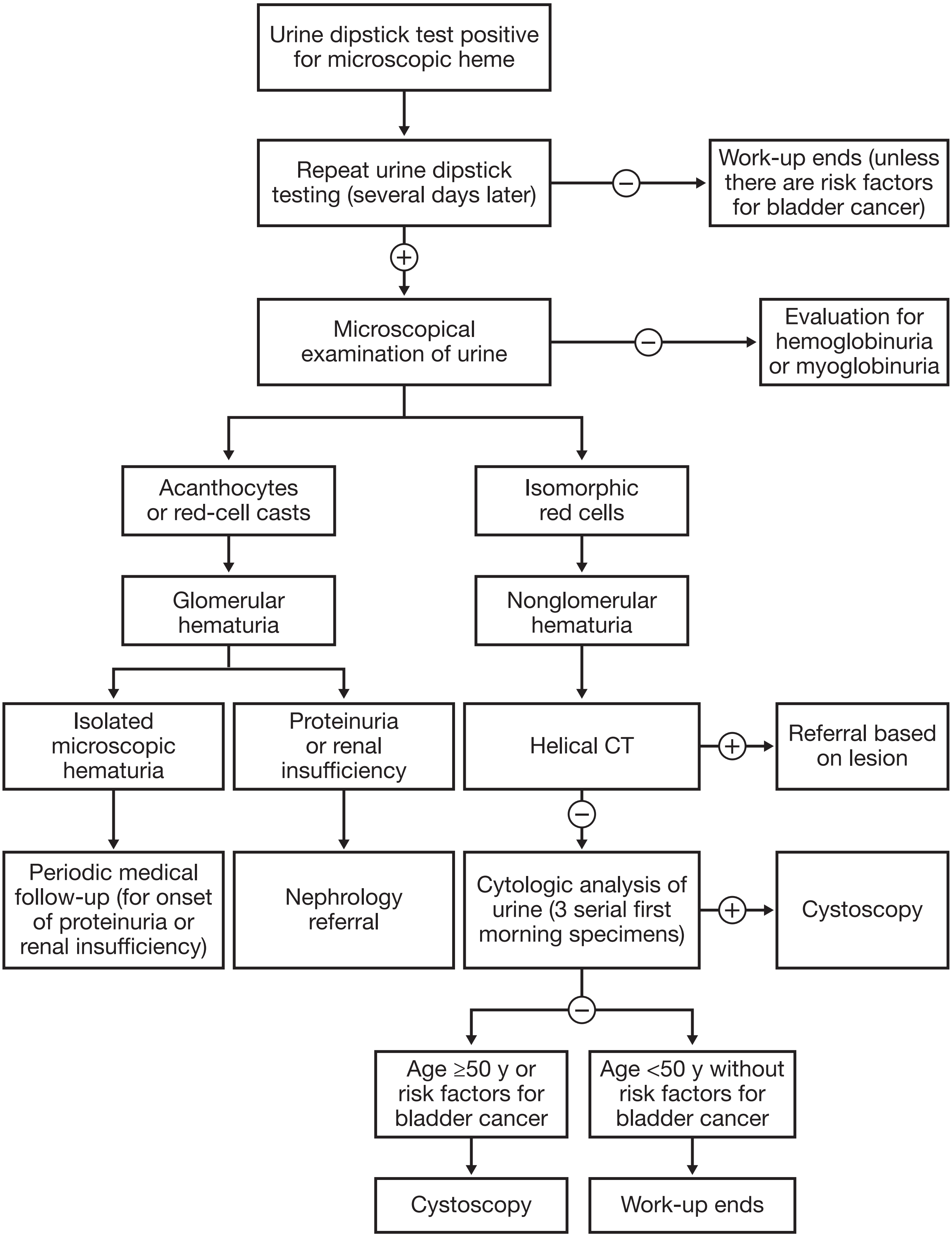
Urine dipstick test positive for microscopic heme
Repeat urine dipstick testing (several days later)
−
Work-up ends (unless there are risk factors for bladder cancer)
+
Microscopical examination of urine
−
Evaluation for hemoglobinuria or myoglobinuria
Acanthocytes or red-cell casts
Isomorphic red cells
Glomerular hematuria
Nonglomerular hematuria
Isolated microscopic hematuria
Proteinuria or renal insufficiency
Helical CT
+
Referral based on lesion
−
Periodic medical follow-up (for onset of proteinuria or renal insufficiency)
Nephrology referral
Cytologic analysis of urine (3 serial first morning specimens)
+
Cystoscopy
−
Age ≥50 y or risk factors for bladder cancer
Age <50 y without risk factors for bladder cancer
Cystoscopy
Work-up ends

Figure 67.1. *Evaluation of Microscopic Hematuria. If hematuria is determined to be nonglomerular in origin, computed tomography (CT) should be performed without contrast medium if a stone is suspected to be present, or first without and then with contrast medium if no stone is suspected. Ultrasonography should be performed instead of CT in pregnant patients and those with hypersensitivity to contrast medium. Risk factors for bladder cancer include cigarette smoking, occupational exposure to chemicals used in certain industries (leather, dye, and rubber or tire manufacturing), heavy phenacetin use, past treatment with high doses of cyclophosphamide, and ingestion of aristolochic acid found in some herbal weight-loss preparations. Plus signs indicate positive findings; minus signs, negative findings.*

(From Cohen RA, Brown RS. Clinical practice: microscopic hematuria. N Engl J Med. 2003 Jun 5;348(23):2330-8; used with permission.)

KEY FACTS

- ✓ Testicular cancer—seminoma or nonseminoma
- ✓ Nonseminomatous component with a seminoma—treat like a nonseminoma
- ✓ Testicular cancer evaluation—
  - determine β-HCG, AFP, and lactate dehydrogenase levels
  - perform CT of the abdomen (retroperitoneal lymph nodes) and chest (mediastinal lymph nodes or pulmonary nodules)
- ✓ Increased AFP value—rules out pure seminoma; treat tumor like a nonseminoma
- ✓ Management of non–muscle-invasive bladder cancer—periodic cystoscopy and resection of recurrent tumors
- ✓ Kidney cancer—if localized (including some with regional lymph node involvement), treat surgically
- ✓ Cytoreductive nephrectomy—
  - considered even with stage IV disease (unlike with other metastatic cancers)
  - if performed in combination with systemic therapy, it may help some patients live longer

68

Lung Cancer and Head and Neck Cancer

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Lung Cancer

Background

Each year in the United States, approximately 220,000 new cases of lung cancer are diagnosed and approximately 158,000 people die of lung cancer. Lung cancer accounts for approximately 27% of all cancer deaths. Most patients with a new diagnosis of lung cancer are older than 65 years.

About 95% of lung cancers in men and about 80% of lung cancers in women result from cigarette smoking. Men who smoke 1 to 2 packs per day have up to a 25-fold increased risk of lung cancer compared with men who have never smoked. The risk of lung cancer for a former smoker decreases with time. Exposure to secondhand smoke is associated with an increased risk of lung cancer. Certain occupations (eg, smelter and iron work) and exposure to chemicals (eg, arsenic and methylethyl ether), radioactive agents (radon), and asbestos are associated with increased risks of lung cancer. Electronic cigarettes (e-cigarettes) have increased greatly in popularity, yet clear evidence on their safety is lacking.

Histologic Types and Characteristics

Lung cancer is classified histologically into small cell and non–small cell types (Table 68.1). Manifestations of lung cancer are listed in Box 68.1.

Non–small cell lung cancer (NSCLC) can be classified into squamous, adenocarcinoma, and large cell types. Squamous cell carcinoma may be associated with hypercalcemia due to the secretion of parathyroid hormone-related protein. Squamous cell carcinoma tends to occur centrally, whereas large cell and adenocarcinoma types tend to be peripheral. Adenocarcinoma is the most common type of NSCLC and the most frequent histologic subtype in nonsmokers. Patients with adenocarcinoma in situ, minimally invasive adenocarcinoma, and **invasive mucinous adenocarcinoma of the lung** (previously referred to as bronchoalveolar carcinoma) frequently have a patchy infiltrate and recurrent pneumonia.

Small cell lung cancer occurs almost exclusively in smokers and has the poorest prognosis. The primary tumors are often small but are often associated with bulky mediastinal adenopathy and a high rate of distant metastases. They may be associated with paraneoplastic syndromes, such as syndrome of inappropriate antidiuretic hormone (SIADH) and Lambert-Eaton myasthenic syndrome, with the primary clinical manifestation of muscle weakness.

KEY FACTS

✓ Lung cancer in the United States—
  - 220,000 new cases are diagnosed annually
  - 158,000 people die annually
  - most patients with a new diagnosis are older than 65 years
  - cigarette smoking causes 95% of cases in men and 80% of cases in women

✓ Histologic classification of lung cancer—
  - small cell lung cancer
  - NSCLC: squamous cell, adenocarcinoma, and large cell

✓ Squamous cell carcinoma—hypercalcemia may be present (from secretion of parathyroid hormone-related protein)

✓ Occurrence of NSCLC—

- squamous cell carcinoma: central
- large cell and adenocarcinoma types: peripheral

✓ Adenocarcinoma—

- most common type of NSCLC
- most frequent histologic subtype in nonsmokers

✓ Small cell lung cancer—may be associated with paraneoplastic syndromes (eg, SIADH)

Key Definition

Invasive mucinous adenocarcinoma of the lung: *a low-grade NSCLC that often occurs with a patchy infiltrate and recurrent pneumonia.*

Screening

In December 2013, the US Preventive Services Task Force (USPSTF) issued the following lung cancer screening guideline based on the results of recent clinical trials (Ann Intern Med. 2014 Mar 4;160[5]:330-8):

"The USPSTF recommends annual screening for lung cancer with low-dose computed tomography in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery."

Table 68.1 • Histologic Classification of Lung Cancer

Class	Prevalence, %	Subtypes
Adenocarcinoma	40	Acinar, bronchioalveolar, papillary, solid carcinoma with mucus formation, mixed
Squamous cell carcinoma	25	. . .
Small cell carcinoma	20	Pure small cell carcinoma, combined small cell carcinoma
Large cell carcinoma	10	Large cell neuroendocrine, basaloid, lymphoepithelial-like, large cell with rhabdoid phenotype
Adenosquamous carcinoma	<5	. . .
Carcinoid	<5	. . .
Bronchial gland carcinoma	<5	. . .

From Collins LG, Haines C, Perkel R, Enck RE. Lung cancer: diagnosis and management. Am Fam Physician. 2007 Jan 1;75(1):56-63; used with permission.

Box 68.1 • Common Lung Cancer Manifestations

- Primary tumor
  - Chest discomfort
  - Cough
  - Dyspnea
  - Hemoptysis
- Intrathoracic spread
  - Chest wall invasion
  - Esophageal symptoms
  - Horner syndrome
  - Pancoast tumor
  - Phrenic nerve paralysis
  - Pleural effusion
  - Recurrent laryngeal nerve paralysis
  - Superior vena cava obstruction
- Extrathoracic spread
  - Bone pain, fracture
  - Confusion, personality change
  - Increased alkaline phosphatase level
  - Focal neurologic deficits
  - Headache
  - Nausea, vomiting
  - Palpable lymphadenopathy
  - Seizures
  - Weakness
  - Weight loss

From Collins LG, Haines C, Perkel R, Enck RE. Lung cancer: diagnosis and management. Am Fam Physician. 2007 Jan 1;75(1):56-63; used with permission.

Management of Incidental Pulmonary Nodules and Diagnosis of Lung Cancer

Pulmonary nodules (radiographic opacities measuring ≤30 mm in diameter) are frequently encountered incidentally on chest computed tomography (CT). Solid nodules can represent benign granulomas, focal scar tissue, intrapulmonary lymph nodes, or primary or metastatic neoplasm. Subsolid nodules usually are transient and represent infection or hemorrhage but can also represent types of adenocarcinoma.

Recently updated guidelines aim to decrease the number of unnecessary follow-up tests and provide clear management decisions. These guidelines require risk stratification on both patient and nodule characteristics. They do not apply to patients younger than 35 years, immunocompromised patients, or persons with preexisting cancer. These guidelines are summarized in Table 68.2.

If lung cancer is suspected, tissue biopsy is the next step. Appropriate imaging modalities for staging are CT of the chest and abdomen or positron emission tomography (PET) CT. The advantage of PET in potentially operable patients is the decrease in futile thoracotomy when PET detects metastatic disease. Histologic staging of the mediastinal lymph nodes can be done with bronchoscopic biopsies. If central nervous system metastasis is suspected, magnetic resonance imaging of the brain, or alternatively CT of the brain with contrast, is performed.

Treatment

Non–Small Cell Lung Cancer

General treatment approaches for NSCLC depend on the stage and tumor type. Resection is the treatment of choice for clinical stage I or II disease. Stereotactic radiosurgery can be used for patients with stage I lung cancer who, because of comorbid conditions or poor pulmonary function, are not healthy enough for standard surgical resection. Patients with stage III NSCLC are treated with chemoradiotherapy, which may be followed by surgery if the cancer is resectable. The use of adjuvant chemotherapy has been shown to improve survival by

Table 68.2 • 2017 Fleischner Society Guidelines for Management of Incidental Pulmonary Nodules Detected by CT

Radiographic Characteristics of Nodules	Size	Follow-up[a]		
Solid	<6 mm (<100 mm^2)	Single	Low risk	No routine follow-up
			High risk	Optional CT at 12 months
		Multiple	Low risk	No routine follow-up
			High risk	Optional CT at 12 months
	6-8 mm (100-250 mm2)	Single	Low risk	CT at 6-12 months, then consider CT at 18-24 months
			High risk	CT at 6-12 months, then CT at 18-24 months
		Multiple	Low risk	CT at 3-6 months, then consider CT at 18-24 months
			High risk	CT at 3-6 months, then CT at 18-24 months
	>8 mm (>250 mm2)	Single	All	Consider CT at 3 months, PET/CT or biopsy
		Multiple	Low risk	CT at 3-6 months, then consider CT at 18-24 months
			High risk	CT at 3-6 months, then CT at 18-24 months
Ground-glass opacities	<6 mm	No follow-up indicated		
	≥6 mm	CT at 6-12 months to confirm persistence, then CT at 3 and 5 years		
Part-solid	<6 mm	No follow-up indicated		
	≥6 mm	CT at 3-6 months to confirm persistence, then annual CT for 5 years		
Multiple subsolid	<6 mm	CT at 3-6 months; if stable, CT at 2 and 4 years		
	≥6 mm	CT at 3-6 months Subsequent management based on most suspicious nodule		

Abbreviations: CT, computed tomography; PET, positron emission tomography.

[a] Low risk according to the American College of Chest Physicians (ACCP) (estimated risk of cancer <5%) is associated with young age, less smoking, smaller nodule size, regular margins, and location other than the upper lobe. To estimate high risk it is recommended to combine the ACCP intermediate-risk (5%-65% risk) and high-risk (>65% risk) categories. High-risk factors include older age, heavy smoking, larger nodule size, irregular or spiculated margins, and upper lobe location. Persons with intermediate risk share both high- and low-risk factors.

Modified from MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. Radiology. 2017 Jul;284(1):228-43; used with permission.

10% to 12% compared with surgery alone for patients with larger tumors or node-positive disease. The use of adjuvant radiotherapy for select patients with resected stage II or III disease decreases the likelihood of local recurrence. Patients with locally advanced unresectable NSCLC are treated with concurrent chemotherapy and radiotherapy. Although patients with metastatic disease are not cured, studies have shown that the use of chemotherapy improves overall survival and quality of life compared with the best supportive care.

Until recently, chemotherapy was the only option for patients with metastatic NSCLC, but current advances in the understanding of the genetics of lung cancer cells and the development of immunotherapy have expanded the therapeutic options. Results from testing of tumors for targetable genetic alterations and programmed cell death ligand 1 (PD-L1) expression guide the management of metastatic NSCLC.

Mutations in the epidermal growth factor (*EGFR*) gene or rearrangements of the anaplastic lymphoma kinase (*ALK*) or *ROS1* gene occur almost exclusively in adenocarcinoma of the lung and are more frequent in nonsmokers and patients with a minimal smoking history. The US Food and Drug Administration (FDA)-approved oral drugs erlotinib, gefitinib, afatinib, and osimertinib are treatments of choice for stage IV *EGFR*-mutated lung cancers. The FDA-approved drugs crizotinib, ceritinib, and alectinib are targeted oral drugs used to treat metastatic lung cancers that have rearrangements of the *ALK* gene. Crizotinib has been approved for lung cancer with *ROS1* rearrangement. The anti–vascular endothelial growth factor agent bevacizumab, when added to chemotherapy for NSCLC, improves response rate and progression-free survival.

The most recent advance in the treatment of NSCLC is the elucidation of mechanisms to manipulate endogenous antitumor immunity. After the initial recognition of an antigen by a T-cell receptor, the robustness of the immune response is regulated by a balance between inhibitory and costimulatory signals (ie, immune checkpoints). Like many tumors, NSCLC expresses immune checkpoints or their ligands to inhibit antitumor immune responses. PD-L1, one of the most important immune checkpoints, negatively regulates T-cell proliferation through engagement of programmed cell death protein 1 (PD-1) and induces apoptosis of tumor-specific T cells. Immune checkpoint blockade with inhibitors of PD-1 or PD-L1 can lead to striking and durable responses in patients with metastatic NSCLC. Pembrolizumab, nivolumab, and atezolizumab have been approved for the treatment of NSCLC. Based on the level of tumor expression of PD-L1, immunotherapy can be used as first-line or later treatment, whereas the combination of pembrolizumab with chemotherapy has been approved by the FDA for first-line therapy in patients with adenocarcinoma of the lung. The adverse effects of these medications arise from the "unleashing" of the immune system and include hypothyroidism, pneumonitis, and colitis, among others. Proper identification and management of these adverse effects is essential.

Recently, clinical trials have shown that timely incorporation of palliative care services to systemic therapy in patients with metastatic lung cancer can increase both quality of life and survival.

Small Cell Lung Cancer

Treatment of limited-stage small cell lung cancer consists of both chemotherapy and chest radiotherapy. Surgical resection has not been shown to improve survival. For patients who have a complete response to chemotherapy and chest radiotherapy, prophylactic cranial radiotherapy is used to decrease the frequency of recurrence in the central nervous system and possibly improve survival. Prophylactic cranial radiotherapy is associated with the risk of delayed leukoencephalopathy, but this risk can be decreased with the administration of radiotherapy in small-dose fractions without concomitant chemotherapy. For limited-stage small cell disease, the median duration of survival is approximately 20 months; 30% to 40% of patients survive 2 years, and 20% survive 5 years.

Chemotherapy is used for extensive-stage (stage IV) small cell lung cancer. Combination chemotherapy is favored over single-agent therapy. Active drugs include etoposide, cisplatin or carboplatin, cyclophosphamide, doxorubicin, and vincristine; the combination of platinum chemotherapy and etoposide is the most frequently used regimen in the United States. Prophylactic cranial radiotherapy improves survival among patients with extensive disease who respond to chemotherapy. The median duration of survival is approximately 12 months, and 10% or fewer survive 5 years.

KEY FACTS

✓ Treatment of NSCLC—knowledge of cancer cell genetics allows use of drugs that target specific mutations

✓ Mutations in *ALK* and *EGFR*—

- occur almost exclusively in adenocarcinoma of the lung
- occur more frequently in nonsmokers and patients with minimal smoking history

✓ Treatment of limited-stage small cell lung cancer—chemotherapy in combination with chest radiotherapy

Head and Neck Cancer

Presentation

The most common head and neck cancer is squamous cell carcinoma of the upper aerodigestive tract. Head and neck squamous cell carcinoma can occur in the nasopharynx, oropharynx, larynx or hypopharynx, oral cavity, and paranasal

Table 68.3 • Clinical Presentation of Head and Neck Squamous Cell Carcinoma

Subsite	Clinical Presentation
Oral cavity	Sores, ulcers, pain
Oropharynx	Sore throat, chronic dysphagia, odynophagia, otalgia
Hypopharynx	Soreness, dysphagia, otalgia, and hoarseness
Larynx	Persistent hoarseness, shortness of breath
Supraglottis	Neck mass
Nasopharynx	Otitis media unresponsive to antibiotics, unilateral nasal airway obstruction, epistaxis, and cranial nerve palsies

From Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. Mayo Clin Proc. 2008 Apr;83(4):489-501. Erratum in: Mayo Clin Proc. 2008 May;83(5):604; used with permission of Mayo Foundation for Medical Education and Research.

sinuses. Uncommon cancers of the head and neck include salivary gland cancers, esthesioneuroblastoma, melanoma, lymphoma, sarcoma, and paraganglioma. Common symptoms at presentation are related to the head and neck and can include throat pain, ear pain, hoarseness, difficulty swallowing, citrus intolerance, and enlarged cervical lymph nodes (Table 68.3).

Risk Factors

Traditional risk factors for the development of head and neck squamous cell carcinoma include tobacco abuse, alcohol use, and chewing betel nuts (Box 68.2). People who consume low amounts of vegetables and fruits also have a higher risk of head and neck cancer. Nasopharyngeal cancer is often associated with Epstein-Barr virus. Human papillomavirus is a common cause of oropharyngeal squamous cell carcinoma and is now the eighth most common cancer in men in the United States. Patients with tumors related to human papillomavirus have a much better prognosis than patients with tumors related to smoking and alcohol, particularly if the patients have never smoked.

Treatment and Follow-Up

Treatment options for locally advanced head and neck cancer include 1) surgical resection with possible adjuvant radiotherapy, with or without chemotherapy and 2) organ preservation with chemotherapy and radiotherapy. Recurrence can be local or distant and generally happens within 5 years. However, follow-up by the patient's oncologist or otorhinolaryngologist should be lifelong. Patients with 1 head and neck cancer have a 25% risk of a second head and neck cancer as a result of the field cancerization effect. Common late adverse effects of treatment include skin fibrosis, decreased neck range of motion, lymphedema, xerostomia, dental problems, hypothyroidism, and swallowing difficulties.

Box 68.2 • Risk Factors for Head and Neck Cancer

- Substance use
  - Tobacco (primary risk factor)
    - Smoking
    - Chewing
    - Secondhand smoke
  - Alcohol
    - Alcohol and tobacco together (additive effect)
    - Betel nuts
- Dietary
  - Vitamin A deficiency
  - Iron deficiency associated with Plummer-Vinson syndrome
- Viruses
  - Human papillomavirus types 16, 18, and 31
  - Epstein-Barr virus
- Occupational exposure
  - Asbestos
  - Nickel
  - Chromium
  - Radium
  - Mustard gas
  - Byproducts of leather tanning and woodworking

From Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. Mayo Clin Proc. 2008 Apr;83(4):489-501. Erratum in: Mayo Clin Proc. 2008 May;83(5):604; used with permission of Mayo Foundation for Medical Education and Research.

KEY FACTS

✓ Most common head and neck cancer—squamous cell carcinoma of the upper aerodigestive tract

✓ Common risk factors for head and neck squamous cell carcinoma—using tobacco or alcohol and chewing betel nuts

✓ Nasopharyngeal cancer—often associated with Epstein-Barr virus

✓ Prognosis with head and neck tumors caused by human papillomavirus—much better than with tumors caused by smoking or alcohol

69

Oncologic Emergencies and Chemotherapy Complications[a]

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Background

Oncologic emergencies occur at any time during the course of cancer, from its initial manifestation to end-stage disease. Prompt recognition and diagnosis of these emergencies improves survival and quality of life for patients. Throughout evaluation and management of the emergency, the patient's overall condition and prognosis should always be considered, and patients should always be offered relief for pain and other symptoms.

Hypercalcemia

The most common causes of hypercalcemia are malignant processes and primary hyperparathyroidism. Patients with primary hyperparathyroidism have increased serum parathyroid hormone (PTH) values, but PTH is usually suppressed in cancer-associated hypercalcemia. Cancer-related hypercalcemia is often mediated by PTH-related protein (PTHrP), which is secreted by the tumor and can be measured with current assays. In general, however, measuring PTHrP levels is of academic interest only and should not be done on a routine basis. Local osteolytic effects from tumors within bone can cause hypercalcemia in patients with widespread metastatic breast cancer and multiple myeloma but only rarely in patients with prostate cancer. Tumors can also cause hypercalcemia by secreting other bone-resorbing substances or by enhancing conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, a mechanism closely associated with lymphomas.

Accelerated bone resorption is due to activation of osteoclasts by various mediators, primarily PTHrP. The same factors that induce osteoclast-mediated bone resorption also stimulate renal tubular resorption of calcium. The hypercalcemic state interferes with renal resorption of sodium and water, leading to polyuria and eventual depletion of extracellular fluid volume. This reduces the glomerular filtration rate, which further increases the serum calcium level. Immobilization tips the balance toward bone resorption, thus worsening the hypercalcemia.

Symptoms and signs of hypercalcemia involve the gastrointestinal tract (anorexia, nausea, vomiting, and constipation), kidneys (polyuria, polydipsia, and dehydration), central nervous system (cognitive difficulties, apathy, somnolence, or even coma), and cardiovascular system (hypertension, shortened QT interval, arrhythmias, and enhanced sensitivity to digitalis).

Cancers associated with hypercalcemia include squamous cell carcinomas of the lung and the head and neck, breast cancer, renal cell carcinoma, multiple myeloma, and lymphoma. Patients who have breast cancer or myeloma are the most likely to have bony involvement with their disease.

The magnitude of the hypercalcemia and the degree of symptoms are key considerations for the treatment of hypercalcemia. Generally, patients with a corrected serum calcium value of more than 14 mg/dL, mental status changes, or an inability to maintain adequate hydration should be hospitalized for immediate treatment. However, there is no absolute value of serum calcium at which all patients become symptomatic, and relatively high levels may be well tolerated if the rate of increase has been gradual. The serum calcium value should be adjusted for hypoalbuminemia. The conversion formula is to add 0.8 mg/dL to the measured serum total calcium level for every 1 g of serum albumin less than 4 g/dL.

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[a] Portions previously published in Lewis MA, Hendrickson AW, Moynihan TJ. Oncologic emergencies: pathophysiology, presentation, diagnosis, and treatment. CA Cancer J Clin. 2011 Sep-Oct;61(5):287-314. Epub 2011 Aug 19; used with permission.

Patients with clinically symptomatic hypercalcemia almost always have intravascular volume depletion. Initial therapy therefore includes vigorous hydration with intravenously administered normal saline (up to 500 mL/h if heart function is normal). Loop diuretics are not used until after intravascular volume expansion has been completed. Furosemide facilitates urinary excretion of calcium by inhibiting calcium resorption in the thick ascending loop of Henle. Use of thiazide diuretics should be avoided because they can worsen hypercalcemia.

The use of intravenous bisphosphonates (zoledronic acid or pamidronate, which is favored for patients with compromised renal function) is standard therapy for cancer-related hypercalcemia. Use of oral agents should be avoided because absorption from the gastrointestinal tract is poor. Bisphosphonates bind to hydroxyapatite and inhibit osteoclasts. In addition to fluids, bisphosphonates have become the mainstay for treatment of hypercalcemia, but they must be used cautiously and infused over longer periods in patients with renal failure.

Denosumab is a monoclonal antibody directed against the RANK ligand, which stimulates osteoclast activity in metastatic cancers that cause hypercalcemia. In 2014, the US Food and Drug Administration approved the use of denosumab for treatment of cancer-associated hypercalcemia. Studies have reported that denosumab is effective in cases of cancer-associated hypercalcemia that have become refractory to bisphosphonates.

Calcitonin may be given subcutaneously or intramuscularly; the intranasal form does not effectively decrease calcium levels. Calcitonin has a rapid onset of action and often decreases the calcium level within 12 to 24 hours; thus, it is useful in immediate life-threatening situations, such as cardiac arrhythmias or seizures. However, calcitonin is a relatively weak agent with a short-lived effect, and it should not be used as a single agent because of the potential for rebound hypercalcemia. Salmon-derived calcitonin is associated with a risk of hypersensitivity reaction, and epinephrine should be given for any allergic sequelae beyond flushing, but anaphylaxis is so rare that a test dose is no longer recommended.

Glucocorticoids are useful in hypercalcemia associated with calcitriol production by hematologic cancers and can have a direct antitumor effect on neoplastic lymphoid tissue.

Calcium-free hemodialysis may be the fastest and least hazardous method of correcting hypercalcemia in patients with decreased kidney function. Dialysis also allows calcium levels to be lowered in patients who have congestive heart failure or other conditions that prevent high-volume fluid infusion.

Tumor Lysis Syndrome

Tumor lysis syndrome results from the release of tumor cell contents into the bloodstream such that overwhelming concentrations of certain substances become life-threatening. It most commonly occurs with cancers that have large tumor burdens and high proliferation rates that are exquisitely sensitive to chemotherapy. Tumor lysis syndrome rarely occurs spontaneously before antitumor therapy begins. Examples include high-grade lymphomas, leukemia, and, much less commonly, solid tumors (small cell lung cancer, anaplastic thyroid cancer, and germ cell tumors). The syndrome is characterized by hyperuricemia, acidosis, hyperkalemia, hyperphosphatemia, and hypocalcemia. These disturbances can lead to kidney failure, arrhythmias, tetany, coagulation abnormalities, and death. The syndrome can be controlled with adequate hydration, alkalinization, and administration of allopurinol before chemotherapy. Allopurinol does not decrease uric acid levels that are already increased.

A randomized controlled trial comparing prophylaxis with allopurinol versus febuxostat showed minor improvements in some laboratory parameters but no clinical benefit that would justify the significantly higher cost of this medication. Febuxostat could be considered in rare, very-high-risk cases in which the patient has a severe contraindication to the use of allopurinol. Severe hyperuricemia can be treated with rasburicase, which, because of its cost, should be reserved for serious cases.

KEY FACTS

✓ Oncologic emergencies—

- occur at any time during the course of a cancer, from initial manifestation to end-stage disease
- prompt recognition and diagnosis improve patient survival and quality of life
- the patient's overall condition and prognosis should always be considered throughout evaluation and management
- patients should always be offered relief for pain and other symptoms

✓ Hypercalcemia—symptoms and signs involve the gastrointestinal tract, kidneys, central nervous system, and cardiovascular system

✓ Treatment of hypercalcemia—

- hospitalize patients who have a corrected serum calcium value >14 mg/dL, who have mental status changes, or who cannot maintain adequate hydration
- initially hydrate with normal saline intravenously (up to 500 mL/h if heart function is normal)
- also administer bisphosphonates intravenously
- calcitonin may be given subcutaneously or intramuscularly (intranasal calcitonin does not decrease calcium levels)

✓ Tumor lysis syndrome—

- caused by release of tumor cell contents into bloodstream, resulting in overwhelming, life-threatening levels of certain substances
- characterized by hyperuricemia, acidosis, hyperkalemia, hyperphosphatemia, and hypocalcemia
- can result in kidney failure, arrhythmias, tetany, coagulation abnormalities, and death

Key Definition

Tumor lysis syndrome: *life-threatening hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia that result from the release of tumor cell contents into the bloodstream.*

Febrile Neutropenia

Febrile neutropenia is defined as a temperature of 38.3°C or higher on 1 occasion, or 2 episodes of 38.0°C at least 1 hour apart, *and* an absolute neutrophil count of 500×10^9/L or less (or <$1,000\times10^9$/L with a predicted decrease to <500×10^9/L within 48 hours). Febrile neutropenia most commonly occurs after chemotherapy administration; the risk depends on the regimen administered. Febrile neutropenia can also result from any other cause of neutropenia, such as autoimmune conditions, administration of nonchemotherapeutic drugs, or a bone marrow dyscrasia. Although a source of infection is identified in only a minority of patients, any patient with neutropenic fever should have at least 2 sets of peripheral blood samples drawn for cultures, preferably before antibiotics are given. In addition, at least 1 blood sample for culturing should be drawn through each lumen of a multiple-port vascular catheter to determine whether the infection is device related.

Key Definition

Febrile neutropenia: *temperature ≥38.3°C on 1 occasion, or 2 episodes of 38.0°C ≥1 hour apart, and an absolute neutrophil count ≤500×10^9/L (or <$1,000\times10^9$/L with a predicted decrease to <500×10^9/L within 48 hours).*

Although management of febrile neutropenia generally involves hospitalization and institution of parenteral broad-spectrum antibiotics, recent extensive clinical experience and multiple randomized controlled trials have shown that outpatient therapy is safe and efficacious for select patients. All patients need to be evaluated by a physician for both medical and social contraindications to outpatient treatment (Box 69.1). Patients who have no contraindications to outpatient treatment should receive oral amoxicillin-clavulanate 875 mg twice daily and oral ciprofloxacin 500 mg every 8 hours. All patients should be reevaluated within 24 hours either by telephone contact or in person.

Box 69.1 • Medical and Social Contraindications to Outpatient Treatment of Febrile Neutropenia

- Medical contraindications
  - Anticipated duration of neutropenia of >7 d (typically patients with leukemia or lymphoma)
  - Absolute neutrophil count ≤0.10×10^9/L
  - Comorbid medical conditions
    - Hypotension (systolic blood pressure <90 mm Hg)
    - Hypoxia or tachypnea (respirations >30/min)
    - Altered mental status
    - Renal insufficiency (creatinine >2.5 mg/dL)
    - Hyponatremia (sodium <124 mmol/L)
    - Bleeding
    - Dehydration
    - Poor oral intake
- Social contraindications
  - History of nonadherence to medical therapy or being unreliable with prior medical therapy follow-up
  - Geographically remote (>50 km from 24-h emergency medical care)
  - Unable to care for self and lack of reliable caregiver
  - No telephone
  - No transportation

For inpatients with febrile neutropenia, monotherapy is acceptable only with a sufficiently broad-spectrum agent that has activity against *Pseudomonas*, such as a fourth-generation cephalosporin (eg, cefepime), a carbapenem (but not ertapenem because of poor *Pseudomonas* coverage), or piperacillin-tazobactam. Vancomycin can be added for skin and soft tissue infections, pneumonia, or suspicion of an infected device, but it should not be used as monotherapy. Antifungal agents should be added to the regimen if patients have a persistent fever for more than 72 hours while receiving standard broad-spectrum antibiotics or if patients have a prior history of fungal sepsis.

Multiple randomized, placebo-controlled trials have shown that administering colony-stimulating factors at the time of febrile neutropenia does not improve outcomes. Patients who have had prior episodes of febrile neutropenia should receive prophylactic growth factors after subsequent doses of chemotherapy; this has been shown to decrease the risk of febrile neutropenia.

Spinal Cord Compression

Acute spinal cord compression is a neurologic emergency. It usually results from epidural extension of vertebral body metastases from lung, breast, prostate, myeloma, or kidney tumors. Occasionally, compression occurs from tumor invasion through the intervertebral foramen, as seen with lymphoma, sarcomas, and lung cancers in the paraspinous spaces. Occurrence varies by location: 10% of cases occur in the cervical spine, 70% in the thoracic spine, and 20% in the lumbar spine. Multiple noncontiguous levels are involved in 10% to 40% of cases. The most important prognostic factor in preserving neurologic function is early diagnosis, before neurologic deficits have developed.

More than 90% of patients have associated pain. Cervical pain may radiate down the arm. Thoracic pain radiates around the rib cage or abdominal wall; it may be described as a compressing band bilaterally around the chest or abdomen. Lumbar pain may radiate into the groin or down the leg. Pain may be aggravated by coughing, sneezing, or straight-leg raising. Focal neurologic signs depend on the level affected. Paresthesias (tingling and numbness), weakness, and altered reflexes also can be present (Table 69.1). Tenderness over the spine may help localize the level, but absence does not exclude the possibility of spinal cord involvement. Autonomic changes in urinary or fecal retention or incontinence are very concerning and may predict development of motor function loss in the near future.

Imaging studies include bone scans or plain radiography, which show vertebral metastases in approximately 85% of patients with epidural compression. Magnetic resonance imaging (MRI) of the entire spine is generally recommended. Computed tomography (CT) myelography can be used if patients cannot undergo MRI.

Treatment usually includes an initial bolus of dexamethasone intravenously. The exact dose is controversial, ranging from 10 to 100 mg. Higher initial doses are associated with more adverse effects and are not clearly associated with improved outcomes. Thereafter, dexamethasone is given (4 mg 4 times daily), although some physicians favor higher doses for a few days before a rapid taper. Radiotherapy to the involved areas is considered standard, but chemotherapy can also be effective for sensitive tumors (germ cell tumors and lymphomas). The Patchell criteria are used to identify patients who are likely to benefit from emergent surgical resection and stabilization (Box 69.2). Patients with extensive organ involvement, progressive malignant processes, a life expectancy of less than 3 months, or poor performance status are unlikely to be able to tolerate an extensive operative procedure and should be treated more conservatively.

Cardiac Tamponade

Pericardial effusions are commonly seen with malignant processes, particularly those involving the chest (lymphoma, breast cancer, lung cancer, or metastatic tumors), but cardiac tamponade is rare. Patients initially have chest pain, dyspnea, pulsus paradoxus, and electrical alternans on electrocardiography. The hallmark of true tamponade physiology is end-diastolic collapse of the right ventricle on echocardiography. Treatment is pericardiocentesis, which often rapidly relieves symptoms. Pericardial sclerosis or leaving the pigtail drain in place can prevent reaccumulation of the fluid during treatment of the underlying cancer.

Malignant Airway Obstruction

Malignant airway obstruction can occur with any cancer, but it occurs most commonly with lung or mediastinal tumors, such as lymphoma or germ cell tumor. It presents with dyspnea, stridor, and wheezing. CT often shows the location of the obstruction. Bronchoscopy can be both diagnostic and therapeutic, with use of either laser or stents to open the bronchus. Tissue can also be obtained for diagnosis.

Intracranial Mass Lesions

Brain involvement from primary or metastatic lesions can lead to increased intracranial pressure and mass effect. This can be exacerbated by acute hemorrhage into a tumor (most

Table 69.1 • Reflexes and Their Corresponding Roots and Muscles

Reflex	Root(s)	Muscle
Biceps	C5-6	Biceps
Triceps	C7-8	Triceps
Knee jerk	L2-4	Quadriceps
Ankle jerk	S1	Gastrocnemius

Box 69.2 • Patchell Criteria for Decompressive Surgery in Patients With Malignant Spinal Cord Compression (MSCC)

Inclusion criteria

- Age ≥18 y
- Tissue-proven diagnosis of cancer (not of CNS or spinal column origin)
- MRI evidence of MSCC (displacement of the spinal cord by an epidural mass)
- Any neurologic sign or symptom (including pain)
- Not paraplegic for >48 h
- MSCC restricted to 1 area (can include several contiguous spinal or vertebral segments)
- Expected survival of ≥3 mo
- General medical status acceptable for surgery

Exclusion criteria

- Multiple discrete lesions
- Radiosensitive tumors (lymphomas, leukemia, multiple myeloma, and germ cell tumors)
- Mass with compression of only the cauda equina or the spinal roots
- Preexisting neurologic problems not directly related to MSCC
- Prior radiotherapy that would exclude administration of the study dose

Abbreviations: CNS, central nervous system; MRI, magnetic resonance imaging.

Table 69.2 • Toxic Effects of Common Chemotherapy Drugs

Drug	Toxic Effect	Comment
Anthracyclines		
Doxorubicin	Cardiac	Dose-related over lifetime; may be irreversible
Daunorubicin	Myelosuppression	
Epirubicin	Vesicant	Late secondary MDS or leukemia
Idarubicin		
Mitoxantrone		
Platinum agents		
Cisplatin	Renal insufficiency	
Carboplatin	Peripheral neuropathy	Neuropathy can be irreversible
Oxaliplatin	Myelosuppression	Cold-sensitive neuropathy
	Anaphylaxis	
Taxanes		
Paclitaxel	Peripheral neuropathy	Neuropathy can be irreversible
Docetaxel	Myelosuppression	
	Anaphylaxis	
Antimetabolites		
5-Fluorouracil	Mucositis	Adverse effects can be severe in patients with DPD deficiency
Capecitabine	Diarrhea	
	Hand-foot syndrome	
	Myelotoxicity	
Methotrexate	Myelosuppression	Caution in patients with pleural effusions or ascites
	Pulmonary toxicity	
	Mucositis	
Cytosine arabinoside (ara-C)	Myelosuppression	
Gemcitabine	Myelosuppression	
Pemetrexed	Myelosuppression	
Alkylating agents		
Cyclophosphamide	Myelosuppression	
Ifosfamide	Hemorrhagic cystitis	
Chlorambucil		
Melphalan		
Temozolomide	Pneumocystis pneumonia	
Dacarbazine	Lymphopenia	
Carmustine (BCNU)	Myelosuppression	
Lomustine		
Topoisomerase inhibitors		
Etoposide (VP-16)	Myelosuppression	Secondary MDS or leukemia; occurs sooner than with anthracyclines
	Secondary MDS or leukemia	
	Anaphylaxis	
Vinca alkaloids		
Vincristine	Peripheral neuropathy	Neuropathy can be irreversible
Vinblastine	Vesicant	
Monoclonal antibodies		
Trastuzumab	Cardiac dysfunction	Usually reversible
Pertuzumab	Cardiac dysfunction Diarrhea	Usually reversible
Cetuximab	Rash	
	Diarrhea	
Gemtuzumab ozogamicin	Myelosuppression	
Ibritumomab tiuxetan	Lymphopenia	
Panitumumab	Rash	
	Diarrhea	
Rituximab	Lymphopenia	

Abbreviations: DPD, dihydropyrimidine dehydrogenase; MDS, myelodysplastic syndrome.

commonly in metastatic melanoma, renal cell carcinoma, or primary glioblastoma multiforme). Patients have headache, severe nausea, vomiting, focal strokelike deficits, or seizures. Imaging with noncontrast CT can show areas of hemorrhage and mass effect, and MRI may further define the extent of the lesion. Immediate therapy involves the use of corticosteroids, specifically dexamethasone (the exact dose is controversial, but an initial bolus of 10 to 100 mg may be given). The most rapid way to alleviate severe mass effect is surgical intervention, but consideration must be given to the patient's general condition and overall prognosis. Radiotherapy is commonly used for metastatic or primary tumors.

KEY FACTS

✓ Treatment of febrile neutropenia in outpatients (not all patients need to be hospitalized)—oral amoxicillin-clavulanate 875 mg twice daily and oral ciprofloxacin 500 mg every 8 hours

✓ Treatment of febrile neutropenia in inpatients—

- if monotherapy, must use a broad-spectrum agent with activity against *Pseudomonas* (eg, a fourth-generation cephalosporin, a carbapenem other than ertapenem, or piperacillin-tazobactam)
- vancomycin is not used for monotherapy but may be added for skin and soft tissue infections, pneumonia, or suspicion of an infected device
- add antifungal agents if patient has persistent fever (>72 hours) while receiving broad-spectrum antibiotics or a history of fungal sepsis
- use of colony-stimulating factors does not improve outcomes

✓ Spinal cord compression—

- MRI of the entire spine
- treat with an initial bolus of dexamethasone intravenously
- radiotherapy to the involved area is standard
- chemotherapy can be effective for germ cell tumors and lymphomas
- Patchell criteria are used to identify patients for emergent surgical resection and stabilization

✓ Intracranial mass lesions—dexamethasone is used for immediate therapy

Chemotherapy Complications

Toxic effects of common chemotherapy drugs are summarized in Table 69.2.

X

Questions and Answers

Questions

Multiple Choice (Choose the best answer)

X.1. A 42-year-old premenopausal woman undergoes wide local excision of a 1.2-cm breast tumor along with sentinel lymph node surgery; the tumor is identified as a lymph node–negative, strongly ER- and PR-positive, HER2-negative invasive ductal carcinoma. After completion of chemotherapy and radiation therapy, which next treatment would be best for this patient?

a. Tamoxifen
b. Aromatase inhibitor
c. Trastuzumab
d. Oophorectomy

X.2. A 63-year-old woman has a recent diagnosis of a 3.5-cm, 3 lymph node–positive breast cancer that is ER-positive and HER2-positive. Her oncologist has recommended adjuvant chemotherapy with an anthracycline and a taxane in combination with trastuzumab to decrease her risk of breast cancer recurrence. She has a history of type 2 diabetes mellitus, hypertension, and hypercholesterolemia. She is not limited in any of her daily activities and is symptom free. What testing should she undergo before starting chemotherapy?

a. Exercise stress testing
b. Cardiac catheterization
c. Echocardiography
d. 24-Hour Holter monitoring

X.3. A 56-year-old woman who has not been seen by a physician since she was a child comes in for evaluation of skin findings consistent with dermatomyositis. What is the best next step in management?

a. Age-appropriate cancer screening
b. Serum glucose and hemoglobin A_{1c}
c. Erythrocyte sedimentation rate
d. HIV testing

X.4. An 80-year-old woman with a 100 pack-year history of tobacco use is evaluated for hemoptysis, weight loss, and dyspnea on exertion. She also describes pain and swelling in her knees and ankles. Radiographs are obtained and show subperiosteal new bone formation. What is the most likely diagnosis?

a. Leukocytoclastic vasculitis
b. Sweet syndrome
c. Hypertrophic osteoarthropathy
d. Polymyalgia rheumatica

X.5. A 66-year-old postmenopausal (for 12 years) woman comes in for evaluation of intermittent vaginal bleeding. Pelvic examination findings are unremarkable. What is the best next step in management?

a. Offer reassurance
b. Repeat pelvic examination in 6 months if symptoms have not resolved
c. Pelvic ultrasonography
d. Papanicolaou and human papillomavirus cotesting

X.6. A 65-year-old woman seeks care for bloating, early satiety, and fatigue. Imaging shows a 6-cm mass on the left ovary and omental nodularity. Chest computed tomography (CT) shows no lung nodularity, enlarged lymph nodes, or effusions. Laboratory tests indicate normal kidney and liver function and a CA 125 value of 500 U/mL. Her medical history is notable for hypertension that is well controlled with her current medications. What is the best next step in management?

a. Obtain a CT-guided biopsy of the ovarian mass.
b. Refer to a gynecologic surgeon for debulking and staging surgery.
c. Initiate therapy with systemic carboplatin and paclitaxel.
d. Initiate therapy with intraperitoneal cisplatin and paclitaxel.

X.7. A 65-year-old woman underwent a surgical debulking procedure by a gynecologic oncologist for recently diagnosed ovarian cancer. Pathologic findings were consistent with a high-grade serous carcinoma involving the right ovary, 3 pelvic lymph nodes, and the omentum. The debulking procedure was optimal, with no visible residual disease at the end of surgery. What is the most appropriate next step in management?

a. Follow-up every 3 months with imaging and CA 125 measurement
b. Abdominal and pelvic radiotherapy
c. Abdominal radiotherapy
d. Adjuvant chemotherapy

X.8. A 62-year-old man is found to have microcytic anemia on workup for fatigue. Colonoscopy shows a lesion in the ascending colon, and a biopsy confirms adenocarcinoma. Staging computed tomography shows no sign of metastatic disease. He undergoes a right hemicolectomy, and no adjuvant therapy is recommended. How often should the patient have surveillance colonoscopy?

a. Yearly for 5 years, then every 5 years thereafter
b. One year after surgery, 4 years after surgery, then every 5 years thereafter
c. Every 5 years after surgery
d. Every 2 years for 10 years, then every 5 years thereafter

X.9. A 56-year-old woman seeks care for a 1-month history of hematochezia. Her hemoglobin level is 7.9 g/dL. Colonoscopy shows a lesion in the proximal rectum. Staging computed tomography shows 2 lesions in the liver and no other sites of metastatic disease. Biopsy of the rectal tumor and a liver lesion both indicate adenocarcinoma. What is the best next step in management?

a. Surgical removal of the rectal tumor to prevent further blood loss
b. Concurrent chemotherapy and radiation therapy to the rectal tumor
c. Systemic chemotherapy and an antiangiogenesis inhibitor for treatment of the primary tumor and the metastatic disease
d. Assessment by a liver surgeon to determine if the patient is a candidate for curative resection of the metastatic disease

X.10. A 44-year-old woman was found to have an adenocarcinoma in the descending colon on surveillance endoscopy for ulcerative colitis diagnosed at age 20 years. She subsequently underwent a left hemicolectomy and, on pathologic review, was found to have 7 lymph nodes involved with micrometastatic disease. Six months of adjuvant therapy with capecitabine plus oxaliplatin is recommended. Which is the most likely long-term adverse effect of the adjuvant chemotherapy?

a. Chronic diarrhea
b. Chronic daily headache
c. Peripheral neuropathy
d. Palmar-plantar dysesthesia

X.11. A 43-year-old man seeks care for low back pain. After several weeks of conservative therapy, his back pain has increased in intensity. Lumbar spine radiographs show several lytic lesions. His β_2-microglobulin level is normal, and his prostate-specific antigen (PSA) level is 2,563 ng/mL. A bone scan shows diffuse skeletal metastases, and computed tomography of the abdomen and pelvis is negative for lymphadenopathy or visceral metastases. Chest radiography shows normal findings. After a diagnosis of metastatic prostate cancer is confirmed, what is the initial step in his treatment?

a. Radiation therapy to the painful bone metastases
b. Androgen deprivation therapy
c. Chemotherapy
d. Prostatectomy to remove the primary tumor

X.12. A 25-year-old man seeks care for a progressively enlarging, mildly tender right testicular mass. He has no urinary symptoms, and examination shows a palpable solid mass on the posterior aspect of the right testicle. Left testicular examination findings are negative. There are no palpable inguinal lymph nodes. Abdominal examination findings are negative. What is the best next step in evaluating this testicular mass?

a. Transscrotal aspiration and biopsy of the mass
b. Computed tomography (CT) of the abdomen and pelvis
c. Serum β-human chorionic gonadotropin, alpha fetoprotein, and lactate dehydrogenase measurement
d. Testicular ultrasonography

X.13. A 67-year-old man with a medical history significant for tobacco abuse seeks care for a productive cough and occasionally blood-tinged sputum. For the past few weeks he has been constipated and has had abdominal pain. He feels extremely fatigued. Chest radiography shows a 3-cm right lower lobe spiculated mass. Results of complete blood count are normal, and his other laboratory values are significant for a calcium level of 12.3 mg/dL. What is the most likely diagnosis?

a. Small cell lung cancer
b. Adenocarcinoma of the lung
c. Metastatic colon cancer
d. Squamous cell lung cancer

X.14. A 65-year-old woman seeks care from her primary care provider for increased fatigue and somnolence. She has severe chronic obstructive pulmonary disease and still smokes 1 pack of cigarettes per day. She has had 12 pounds of unintentional weight loss in the past 2 months. Laboratory test results are significant for a serum sodium value of 125 mEq/L, plasma osmolality of 272 mOsm/kg, and urine osmolality of 206 mOsm/kg. Chest radiography shows a 6-cm right hilar mass. What is the most likely diagnosis?

a. Metastatic breast cancer
b. Small cell lung cancer
c. Adenocarcinoma of the lung
d. Sarcoidosis

X.15. A 72-year-old man reports cough and fatigue. Computed tomography (CT) of the chest shows a 5-cm right hilar mass. Biopsy of the mass indicates small cell lung cancer. Positron emission tomography (PET) CT shows that the mass is PET avid, but no other disease is seen. Magnetic resonance imaging of the head is negative for metastasis. Otherwise, he has no medical problems other than nicotine dependence. What is the next step in management?

a. Surgery
b. Observation
c. Palliative care
d. Combination chemotherapy and radiation

X.16. A 23-year-old man has acute lymphoblastic leukemia and is started on chemotherapy. Twenty-four hours after administration of the first dose of chemotherapy he begins to have increased confusion and seizurelike activity. Laboratory test results show potassium 7.2 mg/dL, creatinine 3.1 mg/dL, calcium 5.4 mg/dL, lactate dehydrogenase 450 U/L, and uric acid 15 mg/dL. He has had no urine output in the past 2 hours. What is the best next step in management?

a. Rasburicase
b. Allopurinol
c. Febuxostat
d. Furosemide

X.17. A 64-year-old woman has acute onset of back pain and bilateral leg weakness. She had been fully active up until this acute event. She was treated 12 years ago for a stage I estrogen receptor–positive breast cancer with surgery, radiotherapy, chemotherapy, and 5 years of hormonal therapy. In the past 7 years, she has had no evidence of recurrent disease and has regular evaluations with her oncologist and primary care physician. On examination, she is in obvious pain. General examination findings are benign, and neurologic examination shows symmetric strength in both lower extremities. Magnetic resonance imaging of the cervical, thoracic, and lumbar spine shows what appears to be a pathologic fracture at the T10 vertebral body, with compression of the thecal sac, but no other bony lesions are noted. She has no other comorbid illnesses and takes no medications at this time. In addition to pain medication and dexamethasone, what is the best next step in management?

a. Spine consultation for consideration of decompressive operation
b. Biopsy of suspected lesion
c. Radiation therapy referral
d. Systemic chemotherapy

Answers

X.1. Answer a.

Tamoxifen is effective adjuvant therapy for women who are either premenopausal or postmenopausal at diagnosis. Aromatase inhibitors are appropriate only for postmenopausal women, even if chemotherapy-induced amenorrhea develops in a premenopausal woman. An aromatase inhibitor in this scenario can cause her ovaries to begin to function again, which would be detrimental to her prognosis. Trastuzumab is not indicated in HER2-negative disease. Therapeutic oophorectomy or ovarian suppression with a gonadotropin-releasing hormone analogue has been studied in combination with aromatase inhibitors or tamoxifen as adjuvant therapy, but oophorectomy alone is not standard adjuvant therapy.

X.2. Answer c.

Patients receiving anthracyclines and/or trastuzumab should undergo echocardiographic assessment of left ventricular (LV) function. Anthracyclines are known to cause a late-onset, dose-dependent, irreversible decrease in cardiac contractility. Trastuzumab can also cause a decrease in LV contractility, but fortunately this is often transient and can recover with drug discontinuation. Many patients can even be rechallenged with trastuzumab if their LV function returns to normal. Stress testing, cardiac catheterization, and 24-hour Holter monitoring have no routine role in screening for baseline cardiac function.

X.3. Answer a.

Approximately one-third of patients with dermatomyositis have an underlying malignant process as the cause. Therefore, age-appropriate screening for an underlying cancer would be important for this patient. Measurement of serum glucose, hemoglobin A_{1c}, and erythrocyte sedimentation rate and HIV testing may be appropriate as a part of this patient's general evaluation but would not help determine the underlying cause of the patient's dermatomyositis.

X.4. Answer c.

This patient's radiography findings, symptoms, and probable intrathoracic tumor make the diagnosis of hypertrophic osteoarthropathy most likely. Leukocytoclastic vasculitis presents as ulceration, cyanosis, and pain over affected regions. Sweet syndrome involves erythematous nodules of the skin and is associated with leukemias and lymphomas. Polymyalgia rheumatica presents with limb girdle pain and stiffness and increased serum erythrocyte sedimentation rate. It is associated with multiple types of neoplasms including leukemia, lymphoma, myelodysplastic syndromes, colon, lung, renal, prostate, and breast cancers.

X.5. Answer c.

Postmenopausal bleeding must be evaluated with a pelvic examination, pelvic ultrasonography, and/or endometrial biopsy. Observation is not appropriate. Persistent bleeding must be evaluated immediately rather than being re-evaluated in 6 months. Papanicolaou and human papillomavirus cotesting would not help in determining the cause of postmenopausal bleeding.

X.6. Answer b.

This patient should be referred to a gynecologic surgeon for debulking and staging surgery in a timely manner. Her imaging findings and CA 125 levels are consistent with ovarian cancer, so she does not need a CT-guided biopsy of the mass. Because she has minimal medical comorbid conditions, is in good health, and has a disease pattern that is most likely resectable, the recommendation would be surgery before chemotherapy. Intraperitoneal therapy is only offered after optimal surgery. If systemic chemotherapy is recommended before surgery, tissue confirmation via biopsy or laparoscopy is required before starting chemotherapy.

X.7. Answer d.

Unless the tumor is grade 1 and confined to the inside of the ovary (no surface involvement), adjuvant chemotherapy is required for the treatment of ovarian cancer. Observation is not an option for her because her disease had spread outside the ovary. Radiation is not used in first-line therapy for ovarian cancer.

X.8. Answer b.

The current recommendations for endoscopic surveillance after resection of colorectal cancer is colonoscopy 1 year after surgery, then 4 years after surgery, then every 5 years for as long as it is believed that the patient would be a candidate for surgical or chemotherapeutic intervention if a new lesion is found.

X.9. Answer d.

Patients with colorectal cancer with oligometastatic disease should have a surgical consultation to determine whether the metastatic lesions are amenable to surgical resection. The choice of systemic therapy is dependent on the results of the surgical consultation, and the trend is for patients to receive systemic chemotherapy, with or without a biologic agent, before surgery depending on the extent of disease. Patients who are not candidates for surgical resection typically start with systemic therapy and forego radiation therapy. Treatment with systemic therapy typically leads to cessation of hematochezia; therefore, emergent surgery to remove the primary tumor may not be necessary.

X.10. Answer c.

Chemo therapy-induced peripheral neuropathy is a common, long-lasting adverse effect of the platinum chemotherapeutic agents. The severity of the peripheral neuropathy typically wanes over time, but approximately 20% of patients have long-term numbness and tingling. Diarrhea, headache, and palmar-plantar dysesthesia are common adverse effects related to administration of fluoropyrimidines, including capecitabine. Although these effects occur frequently during chemotherapy administration, they are typically short term and resolve within several weeks after discontinuation of therapy.

X.11. Answer b.

This patient has metastatic hormone-sensitive adenocarcinoma of the prostate. The initial step in controlling the disease is androgen deprivation therapy. In patients with significant bony metastases, there is concern about an initial rapid increase in PSA level (called a PSA flare) and exacerbation of pain with the initial androgen deprivation therapy. This can be avoided by either starting with an injection of a luteinizing hormone–releasing hormone (LHRH) antagonist or using an LHRH agonist concurrently with an oral antiandrogen such as bicalutamide for the first month of treatment. Radiation of painful bone metastases is an option in the setting of metastatic prostate cancer but is not the initial step. Androgen deprivation therapy itself may help to reduce bone pain. If it does not, pain medications can be used to help reduce pain from bony metastatic disease. If certain areas are still painful despite medical therapy, then palliative radiation can be considered for painful bony metastases. For men who are considered to have high-volume metastatic disease, docetaxel chemotherapy is now an option in the hormone-sensitive setting, if they are otherwise fit for chemotherapy. Therefore, this patient would most likely be treated with chemotherapy, although it would not be the first step. Typically, chemotherapy must be started within the first 120 days of the patient receiving androgen deprivation therapy. In the setting of metastatic disease, there is no evidence that prostatectomy to treat the primary prostate tumor will help with disease control or alter the natural history of the cancer.

X.12. Answer d.

His age, along with the finding of a solid palpable mass in the testicle, is concerning for testicular cancer. The next step in his care is testicular ultrasonography and, if this reveals concerning findings for a solid testicular mass, the patient should be referred to a urologist. If there is a high enough index of suspicion for testicular cancer based on the ultrasonography findings, or certainly if testicular cancer is confirmed with orchiectomy, then appropriate work-up would include CT of the abdomen and pelvis, chest imaging, and evaluation of serum tumor markers. Even for suspicious testicular lesions, biopsy should not use a transscrotal approach because of concern for seeding the hemiscrotum with malignant cells if the mass is, in fact, testicular cancer.

X.13. Answer d.

Hypercalcemia is a common paraneoplastic syndrome of squamous cell lung cancer. It is mediated through parathyroid hormone-related protein, which simulates most of the actions of parathyroid hormone, including increases in bone resorption and distal tubular calcium reabsorption. Small cell lung cancer, adenocarcinoma of the lung, and metastatic colon cancer are not typically associated with hypercalcemia.

X.14. Answer b.

The patient has impaired water excretion that leads to dilutional hyponatremia. Syndrome of inappropriate antidiuretic hormone (SIADH) is commonly seen in patients with small cell lung cancer. Metastatic breast cancer, adenocarcinoma of the lung, and sarcoidosis are not typically associated with SIADH.

X.15. Answer d.

The patient has limited-stage small cell lung cancer. This is treated with a combination of chemotherapy and radiotherapy. There is limited value of surgery in the treatment of small cell lung cancer. Observation and palliative care would not be appropriate options at this time.

X.16. Answer a.

The patient has tumor lysis syndrome and needs emergent reversal of this life-threatening condition. Rasburicase can rapidly reverse the severe hyperuricemia that is causing the renal insufficiency and other electrolyte abnormalities. In addition, the patient will need adequate hydration. Allopurinol and febuxostat do not decrease uric acid levels that are already increased. Furosemide should not be given until volume depletion is corrected.

X.17. Answer a.

The patient meets Patchell criteria as an excellent candidate for a decompressive and spinal stabilization procedure. This procedure has led to improved clinical outcomes in functional status and improved overall survival in patients with metastatic cancer. In addition, because it has been 12 years since her original diagnosis, tissue for study could be obtained at the time of decompressive operation. She would most likely benefit from radiation postoperatively, but there is a greater chance of return of neurologic function with an operation. Chemotherapy would not be indicated with relatively limited metastatic disease, especially if this is still estrogen receptor positive.

Section

XI

Psychiatry

70

Mood and Anxiety Disorders

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Since 30% to 40% of ambulatory primary care visits have a psychiatric component, successful patient care often hinges on successful treatment of comorbid psychiatric illness.

The key concept when assessing psychiatric symptoms is whether a symptom interferes with a patient's functioning or causes distress, or both. For example, a patient may have a fear of heights. If this acrophobia never causes an alteration in activity, intervention is unnecessary. If, however, this acrophobia causes distress and interferes with the patient's functioning, intervention may be warranted.

Mood Disorders

Mood disorders are common, with a prevalence of 8% in the general US population. The essential feature is disturbance of mood in a constellation of other symptoms (mood change alone, such as sadness, is not an illness). Mood disorders are accompanied by related cognitive, psychomotor, neurovegetative, and interpersonal difficulties. They may be related to a general medical condition or may be substance induced.

Depressive Disorders

Major Depression

Major depression is a serious psychiatric disorder with primary symptoms that include 5 of the 9 criteria for a major depressive episode for at least 2 weeks (Box 70.1). Acute mood changes (lasting <2 weeks) from medical causes, such as acute blood loss, are not major depression. The lifetime prevalence of depression is 20% for women and 12% for men. For women, the peak age at onset of depression is 33 to 45 years; for men, more than 55 years.

If delusions or hallucinations are also present, they are usually less prominent than in schizophrenia and are understandable in the context of the disordered mood (eg, thoughts of excessive guilt or worthlessness). The disorder is referred to as major depression with psychotic features. These features increase the likelihood of medical treatment resistance (although they predict a better response to electroconvulsive therapy [ECT]).

Box 70.1 • Criteria for a Major Depressive Episode[a]

Depressed mood (feeling sad or empty; tearful)[b]
Diminished interest or pleasure in many activities[b]
Notable weight loss or weight gain (>5% of body weight in 1 mo) or decreased or increased appetite
Insomnia or hypersomnia nearly every day
Psychomotor agitation or retardation
Fatigue or loss of energy
Feelings of worthlessness or inappropriate guilt (which may be delusional)
Diminished ability to think or concentrate, or indecisiveness
Recurrent thoughts of death, including suicidal ideation or planning

[a] Symptoms must be present every day or nearly every day for at least 2 weeks. A diagnosis of major depression requires 5 of these 9 criteria.

[b] A diagnosis of major depression requires either a depressed mood or a loss of interest or pleasure in activities.

Seasonal Affective Disorder

Seasonal affective disorder is a subtype of major depression characterized by the onset of symptoms in autumn or winter. It is twice as common in women as in men and is associated with psychomotor retardation, hypersomnia, overeating (carbohydrate craving), and weight gain (resembling hibernation). Diagnosis requires 3 consecutive years of autumn or winter episodes that resolve by spring or summer. Treatment has relied primarily on phototherapy with a full-spectrum light source of

10,000 lux, which must be used for a minimum of 30 minutes daily in the morning. Antidepressant agents are also of benefit in treatment of this disorder.

Postpartum Depression

Postpartum depression affects 10% of mothers. Although it occurs in all socioeconomic groups, single or poor mothers are at greatest risk. Untreated postpartum depression can adversely affect parent-child bonding. Treatment with antidepressants, although effective, must be balanced with the possible effect on a developing fetus or breast-fed infant, but it is generally accepted that in moderate to severe depression, the risks of not treating depression far outweigh the risk of treatment with most antidepressants. Prescribing clinicians should be cognizant of the pregnancy category of the agent they prescribe in this patient group. Bipolar disorder is overrepresented in patients with postpartum mood disorders, and postpartum psychosis is nearly always a marker of bipolar disorder.

Dysthymia

Dysthymia is chronic depression that is milder in severity than major depression. It can be disabling for the person because the depressed mood is present most of the time during at least a 2-year period. Many patients have 1 or 2 associated vegetative signs, such as disturbance of sleep and appetite. In addition, patients often feel inadequate, have low self-esteem, and struggle with interpersonal relationships. If onset is in late adolescence, the dysthymia may become intertwined with the person's personality, behavior, and general attitude toward life. Treatment is usually a combination of psychotherapy and pharmacotherapy. Pharmacotherapy may be particularly useful for patients with a family history of mood disorders or for those who have the early-onset form of dysthymia. For patients with dysthymia, superimposed major depressive episodes may develop.

Key Definition

Dysthymia: *chronic depression that is milder in severity than major depression.*

Adjustment Disorder With Depressed Mood

Adjustment disorder with depressed mood is a reaction that develops in response to an identifiable psychosocial stressor (eg, divorce, job loss, family or marital problems). The severity of the adjustment disorder (degree of impairment) does not always parallel the intensity of the precipitating event. The critical factor appears to be the relevance of the event or stressor to the patient and the patient's ability to cope with the stress. In general, these reactions are relatively transient. Although patients generally can be treated by an empathetic primary care physician, the development of extreme withdrawal, suicidal ideation, or failure to improve as the circumstances improve may prompt psychiatric referral. Treatment includes supportive psychotherapy, psychosocial interventions, and, sometimes, use of antidepressant agents.

Principles of Depression Treatment

Treatment modalities for depression are in 3 common, major groups: psychotherapy, pharmacotherapy, and neuromodulation treatments such as ECT. Generally, these therapeutic modalities are used in some combination. Although internists rarely conduct formal psychotherapy, brief cognitive interventions, such as challenging overly perfectionistic beliefs, can be helpful.

The selection of medication is based on the adverse effects profile of the medication and on the personal or family history of a good response to a particular agent. Initially, a patient should use a low dose, followed by titration to a therapeutic dose based on clinical assessment. Blood level determinations of a drug are meaningful only for tricyclic antidepressants (TCAs) used at higher doses. Treatment duration usually extends for a minimum of 6 months after the patient noticeably improves. Patients who have a severe depressive episode or who have experienced 2 or more depressive episodes are at high risk for symptom recurrence if not treated with prophylactic medication. Use of antidepressants should be tapered rather than stopped abruptly when treatment is discontinued. If the response to the first antidepressant agent is minimal, the clinician should reevaluate the diagnosis, change to a different class of drug, or consider ECT.

Mania and Bipolar Disorder

The essential features of a manic episode are the presence of an abnormally euphoric, expansive, or irritable mood associated with 3 of the criteria in Box 70.2 (4 criteria are required if the mood is only irritable). For the diagnosis of bipolar disorder, a patient must have had at least 1 episode of mania (bipolar I disorder) or hypomania (bipolar II disorder). Most patients with bipolar disorder have had recurrent depressive episodes in addition to manic episodes; rarely, patients have mania exclusively. The prevalence of bipolar disorder is estimated to be about 1%. Bipolar disorder occurs about as frequently in women as in men, and the usual age at onset is from the teens to 30 years. A family history of bipolar or another mood disorder is more common among patients with bipolar disorder than among patients with other mood disorders. Some patients do not experience a fully developed manic episode and have fewer symptoms. The term *hypomania* has been introduced to describe this form of bipolar disorder (bipolar II disorder), which generally is challenging to clinicians because its subtle features make it more difficult to recognize, and it may be confused with other psychiatric disorders.

Box 70.2 • Criteria for a Manic Episode[a]

Inflated self-esteem or grandiosity
Less need for sleep (rested after 3 h)
Pressured speech
Flight of ideas
Distractibility
Increase in goal-directed activity or psychomotor agitation
Excessive involvement in pleasurable activities that have a high potential for painful consequences (eg, unrestrained buying sprees, sexual indiscretions, inappropriate financial investments)

[a] Symptoms must be present for at least 1 week (4 days if hypomanic) unless interrupted by treatment. Mood is persistently elevated, expansive, or irritable. The diagnosis of manic episode requires 3 of the 7 criteria (4 are required if the mood is irritable only).

Treatment is aimed at mood stabilization with medication and improved social and occupational functioning. Pharmacotherapy of mania includes lithium carbonate, divalproex sodium, other mood stabilizers, and atypical antipsychotics. Lithium has the added benefit of usefulness in prevention or treatment of bipolar depression. Lamotrigine also is effective in prevention of bipolar depression. Patients with bipolar depression may be treated with lithium carbonate, lamotrigine, or an atypical antipsychotic. (Lurasidone, quetiapine, and olanzapine/fluoxetine combination have US Food and Drug Administration approval.)

Mood Disorders Caused by a General Medical Condition

Mood disorders can be caused by medical illness. Many medical conditions may induce mood changes, so the clinical interview should identify symptoms that coexist with the medical disorder, such as excessive guilt, social withdrawal, or suicidal ideation. These mood changes are more specific for a primary depressive disorder. Medical conditions that may cause mood symptoms include endocrinopathies (Cushing syndrome, Addison disease, hyperthyroidism, hypothyroidism, hyperparathyroidism, and hypoparathyroidism), certain malignancies (lymphomas, pancreatic carcinoma, and astrocytomas), neurologic conditions (Parkinson disease, Huntington disease, and Alzheimer disease), autoimmune conditions (systemic lupus erythematosus), and infections (chronic hepatitis C, encephalitis, mononucleosis, and HIV infection).

Substance-Induced Mood Disorders

The essential feature of a substance-induced mood disorder is a mood disturbance, either depressed or manic, due to the direct physiologic effects of a substance. Many substances can induce mood changes, including medications, toxins, and drugs of abuse. The mood symptoms may occur during the use of or exposure to the substance or during withdrawal from the substance. Medications that have been implicated in the induction of mood disturbances include corticosteroids, interferon, reserpine, methyldopa, carbonic anhydrase inhibitors, stimulants, sedative-hypnotics, benzodiazepines, and narcotics. Long-term use or abuse of alcohol or hallucinogens has also been implicated in inducing a mood disturbance.

KEY FACTS

- ✓ When assessing psychiatric symptoms, the clinician should consider whether the symptom interferes with functioning or causes distress
- ✓ More women (20%) than men (12%) have depression over a lifetime
- ✓ Seasonal affective disorder—twice as likely in women; characterized by psychomotor retardation, hypersomnia, overeating, and weight gain
- ✓ Postpartum depression—if untreated, can prevent a mother from bonding with her child
- ✓ Major treatment modalities for depression—psychotherapy, pharmacotherapy, and neuromodulation treatments such as ECT
- ✓ The diagnosis of bipolar disorder requires at least 1 episode of mania (bipolar I disorder) or hypomania (bipolar II disorder)

Anxiety Disorders

Anxiety symptoms may be misinterpreted as those of medical illness because many of the symptoms overlap (eg, tachycardia, diaphoresis, tremor, shortness of breath, nausea, abdominal pain, chest pain). Autonomic arousal and anxious agitation of a medically ill patient can also be attributed quickly to stress or anxiety when the symptoms may represent pulmonary embolus or cardiac arrhythmia. Common sources of anxiety in the medical setting are related to fears of death, abandonment, loss of function, pain, dependency, and loss of control. The decision by the clinician about when to treat or when to seek psychiatric consultation depends on the assessment of the degree of anxiety. Is the patient able to function in their role without distress or avoidance?

Panic Disorder and Agoraphobia

Panic disorder refers to recurrent discrete episodes of extreme anxiety accompanied by various somatic symptoms, such as dyspnea, unsteady feelings, palpitations, paresthesias, hyperventilation, trembling, diaphoresis, chest pain or discomfort, and abdominal distress. **Agoraphobia** refers to extreme fear of being in places or situations from which escape may be difficult or embarrassing. This fear may lead to avoidance, ultimately causing severe limitations in daily functioning for the patient. Panic disorder is more common in women (prevalence, 2%-3%) than in men (prevalence, 0.5%-1.5%). The usual age at onset is from the late teens to the early 30s. A history of childhood separation anxiety is reported in 20% to 50% of patients. The prevalence is higher for first- and second-degree relatives of a person with panic disorder. Most patients describe their first panic attack as spontaneous. They often go to an emergency department after the first attack, believing that they are having a heart attack or a severe medical problem.

Key Definitions

Panic disorder: *recurrent, discrete episodes of extreme anxiety accompanied by various somatic symptoms.*

Agoraphobia: *extreme fear of being in places or situations from which escape may be difficult or embarrassing.*

Patients with panic attacks may be prone to episodes of major depression. The differential diagnosis of panic disorder includes several medical disorders, such as endocrine disturbances (eg, hyperthyroidism, pheochromocytoma, hypoglycemia), gastrointestinal tract disturbances (eg, colitis, irritable bowel syndrome), cardiopulmonary disturbances (eg, pulmonary embolism, exacerbation of chronic obstructive pulmonary disease, acute allergic reactions), and neurologic conditions (especially conditions such as seizures that are episodic or are associated with paresthesias, faintness, or dizziness).

Several substances of abuse may cause or exacerbate anxiety symptoms. Stimulants (eg, cocaine, amphetamines, caffeine) can fuel anxiety, as can withdrawal from sedating agents (eg, alcohol, benzodiazepines, narcotics). Patients may use alcohol or benzodiazepines to prevent or treat panic symptoms, but regular or high-dose use may result in a cycle of tolerance and withdrawal, paradoxically causing an increase in anxiety symptoms.

Effective treatment for most patients includes the following, alone or in combination: antidepressants (particularly selective serotonin reuptake inhibitor [SSRI] antidepressants and generally not bupropion), cognitive behavioral therapy, and benzodiazepines (short-term use). Alcohol and benzodiazepines may reduce the distress of panic attacks, but symptoms may rebound, potentially leading to substance abuse and, paradoxically, to worsening anxiety.

Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) can be a brief reaction that follows an extremely traumatic, overwhelming, or catastrophic experience, or it may be a chronic condition that produces severe disability. The syndrome is characterized by the following features.

1. Persistent reexperiencing (intrusive memories, flashbacks, nightmares)
2. Avoidance of reminders of the event and often a restricted range of affect
3. Persistently increased arousal (eg, startle response, hypervigilance)

PTSD may occur in adults or children. Its comorbidity is increased with substance abuse, depression, and other anxiety disorders. Patients may be more prone to impulsivity, including suicide. As with other anxiety disorders, treatment is usually a combination of psychotherapeutic and, if necessary, pharmacologic interventions. Again, SSRI antidepressants are the mainstay of treatment; prazosin, a centrally acting α-adrenergic antagonist, has been shown to be effective in the reduction of nightmares.

Generalized Anxiety Disorder

Generalized anxiety disorder is characterized by chronic excessive anxiety and apprehension about life circumstances accompanied by somatic symptoms of anxiety, such as trembling, restlessness, autonomic hyperactivity, and hypervigilance. Treatment is usually a combination of cognitive behavioral psychotherapy and psychopharmacologic modalities.

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder is characterized by 2 features: obsessions (distressing thoughts, ideas, or impulses experienced as unwanted) and compulsions (repetitive intentional behaviors performed in response to an obsession, usually neutralizing the anxiety caused by the obsession).

Prevalence rates are 2% to 3% and are about equal in men and women. The onset of this disorder is usually in adolescence or early adulthood. Obsessive traits are often present before onset of the disorder. The predominant neurobiologic theory for the cause of obsessive-compulsive disorder involves dysfunction of brain serotonin systems.

Pharmacologic treatment of this disorder is with antidepressants that are more selective for effects on the serotonin transmission system. These include clomipramine and SSRI agents (fluvoxamine, fluoxetine, citalopram, escitalopram, paroxetine, and sertraline). Behavioral therapies, especially exposure and response prevention, and some other forms of psychotherapy can also be helpful as primary or adjunctive therapy.

The Suicidal Patient

Emergency medicine physicians are often the first to treat patients who have suicidal ideation or who have attempted or completed suicide. Recognition of risk factors for suicide, a thorough assessment of the psychiatric and medical factors, and urgent intervention are critically important. Although a patient who overdoses with a benzodiazepine may be serious about the intent to die, the person who overdoses with acetaminophen is more at risk for serious medical complications.

Recognition of a suicidal gesture is essential in the evaluation of a patient in an emergency department. Although drug overdoses are the commonest form, alcohol intoxication, single-vehicle crashes, and falls from heights may merit further investigation. Many suicidal patients see a physician the week before the attempt. Risk factors about which the physician needs to be aware include recent psychiatric hospitalization, unemployment, poor physical health, past suicide attempts, family history of suicide (especially of a parent), psychosis, alcoholism, drug abuse, chronic pain syndrome, sudden life changes, loneliness, and the anniversary of an important loss. For example, an older man who is divorced or widowed is at increased risk. More than 50% of completed suicide attempts involve guns; access to firearms should be assessed as part of a standard suicide risk assessment.

Psychopharmacology

Medication is rarely the sole treatment of a psychiatric disorder. Rather, medication is a component of a comprehensive treatment plan. Because psychoactive medications are used in various circumstances for many different indications, the major groups of these agents are discussed below in general terms. The choice of a medication usually is based on its adverse effect profile and the clinical profile of the patient. Each major group comprises many effective drugs, but the drugs differ in terms of pharmacokinetics, adverse reactions, and available routes of administration.

Antidepressants: General Principles

First-generation antidepressants include TCAs and monoamine oxidase inhibitors (MAOIs). Newer-generation antidepressants are not easily grouped by their chemical structure or function; SSRIs are the most widely used of this group.

Although older-generation antidepressants are effective in treating depression, they are associated with adverse reactions that limit their use. TCAs are associated with orthostatic hypotension, anticholinergic adverse reactions, and altered cardiac conduction. MAOIs are effective antidepressants but require special dietary restrictions and attention to interactions with other medications to avoid a hypertensive crisis caused by unmetabolized tyramine.

Antidepressants can be useful in the treatment of depression, panic disorder, obsessive-compulsive disorder, generalized anxiety disorder, social anxiety disorder, PTSD, enuresis, bulimia, and attention-deficit/hyperactivity disorder, among others. TCAs and duloxetine can be beneficial for treating certain pain syndromes.

A complete trial of antidepressant medication consists of 4 to 6 weeks of therapeutic doses before refractoriness is considered. If improvement has occurred with the initial trial of the medication but the patient's condition has not returned to baseline, it may be appropriate to increase the dose of the medication, switch to another medication class, or augment by adding another medication. After clinical improvement has been noted, the medication may need to be used for an extended period.

Concerns about antidepressants potentially causing an increase in suicidal thoughts or behavior have resulted in the development of a black box warning for all antidepressants. This topic is controversial, since several studies have not corroborated this concern. The important clinical point to remember is that patients with depression should be assessed for suicidal thinking whether or not they are taking antidepressant medications.

Benzodiazepines

Benzodiazepines are used most appropriately to treat time-limited anxiety or insomnia related to an identifiable stress or change in sleep cycle. After long-term use (>2 months), therapy with benzodiazepines and related substances should be tapered rather than discontinued abruptly to avoid relapse, rebound, and withdrawal.

Relapse is the return of the original anxiety symptoms, often after weeks to months. *Rebound* is the intensification of the original symptoms, which usually last several days and appear within hours to days after abrupt cessation of drug use. *Withdrawal* includes autonomic and central nervous system symptoms that are different from the original presenting symptoms of the disorder.

Several benzodiazepines have metabolites with long half-lives, so smaller doses are needed for elderly persons, adults with cognitive dysfunction, and children. These patient groups, especially patients with known brain damage, may be prone to paradoxical reactions (ie, anxiety, irritability, aggression, agitation, and insomnia).

Lithium

Lithium is used for bipolar disorder, for recurrent depression, and as an adjunct for depression treatment after ECT. Peak lithium levels occur in 1 to 2 hours, and its half-life is about 24 hours; levels are generally checked 10 to 12 hours after the last dose and 4 to 5 days after a dose change. Common adverse reactions include resting tremor, diarrhea, polyuria, polydipsia, thirst, and nausea (lithium should be taken on a full stomach or the extended-release form should be considered). Use in the first trimester of pregnancy is associated with a potential increase in the frequency of Ebstein anomaly, although this continues to be a rare event. Renal effects generally can be reversed with discontinuation of lithium use; renal function should be monitored throughout lithium use. A hematologic effect can be benign leukocytosis. Hypothyroidism is common with lithium use, and thyroid function should be monitored. Lithium can also affect parathyroid function.

Lithium has a narrow therapeutic index (typically 0.5-1.0 mEq/L), and toxicity (typically >1.5-3.5 mEq/L) can cause renal failure and death. Signs of toxicity include abdominal pain and vomiting, dry mouth, nystagmus and blurred vision, delirium, ataxia, hyperreflexia and fasciculations, and seizures.

Lithium levels are increased by angiotensin-converting enzyme inhibitors, thiazide diuretics, nonsteroidal anti-inflammatory drugs, dehydration, overheating or increased perspiration, and certain antibiotics (tetracycline, spectinomycin, and metronidazole). Levels can be decreased by caffeine and theophylline.

Electroconvulsive Therapy

ECT is the most effective treatment for severely depressed patients, especially those with psychotic characteristics. It is also helpful in the treatment of catatonia and mania and may be used for children and adults. ECT can be administered safely to pregnant women if fetal monitoring is available on-site. A usual course of treatment is 6 to 12 sessions given over 2 to 4 weeks.

ECT no longer has any absolute contraindications, although it has several relative contraindications related to anesthesia risks, intracranial space–occupying lesions, and increased intracranial pressure. Before ECT is administered, the patient should be assessed for cardiovascular function, pulmonary function, electrolyte balance, neurologic status (eg, history of epilepsy), and previous experiences with anesthesia.

KEY FACTS

- ✓ A patient with PTSD keeps reexperiencing the event, avoids reminders of it, and is hypervigilant and easily startled
- ✓ Obsessive-compulsive disorder is a combination of distressing thoughts, ideas, or impulses (obsessions) and repetitive, intentional behaviors performed in response to an obsession to neutralize anxiety (compulsions)
- ✓ Lithium has a number of common adverse reactions—resting tremor, diarrhea, polyuria, polydipsia, thirst, and nausea
- ✓ For severe depression, especially with psychotic features, the most effective treatment is ECT

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Psychotic and Somatic Symptom and Related Disorders

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Psychotic Disorders

Psychosis is a generic term used to describe altered thought and behavior, in which the patient is incapable of interpreting their situation rationally and accurately. Psychotic symptoms can occur in various medical, neurologic, and psychiatric disorders. Many psychotic reactions seen in medical settings are either associated with the use of recreational or prescription drugs or occur in the context of delirium. Some of these drug-induced psychotic reactions are nearly indistinguishable from schizophrenia in terms of hallucinations and paranoid delusions (eg, amphetamine and phencyclidine [PCP] psychoses).

Key Definition

Psychosis: *altered thought and behavior in which the patient is incapable of interpreting their situation rationally and accurately.*

When evaluating psychotic patients, the clinician can explore temporal relationships between illness, medication, and the onset of symptoms, which is often helpful in determining the cause. For example, it would be unusual for schizophrenia to initially manifest in a 70-year-old patient; thus, psychotic symptoms that develop at that age likely have a metabolic, medical, or substance-induced cause. Many brain regions may be involved with the production of psychotic symptoms, but the frontal, temporal, and limbic regions are the more likely regions where abnormalities can produce psychotic features.

Various disorders throughout a person's life may be associated with schizophrenialike psychoses. Examples include genetic abnormalities (a microdeletion of chromosome 22, which causes the velocardiofacial syndrome), childhood neurologic disorders (autism and epilepsy), adult neurologic disorders (narcolepsy), medical and metabolic diseases (infections, inflammatory disorders, endocrinopathies, nutritional deficiencies, uremia, and hepatic encephalopathy), drug abuse, and psychologic stressors.

Schizophrenia is a chronic psychotic illness that likely has many interrelated causes. Psychotic symptoms and altered interpersonal skills typically become evident initially in the teens and the 20s, although sometimes initial presentations are seen in the late 30s or early 40s, particularly in women. Symptoms can be subdivided into positive (delusions and hallucinations) and negative (apathy and amotivation) symptoms. Diagnostic criteria include the presence of delusions and hallucinations; marked decrement in functional level in areas such as work, school, social relations, and self-care; and continuous signs of the disturbance for at least 6 months. Exclusion criteria include a consistent mood disorder component and evidence of a medical cause for the symptoms. Suicide is seen in 5% of patients with schizophrenia, typically early in the illness.

Brief psychotic disorder describes a primary psychotic illness lasting less than 1 month; *schizophreniform disorder* is a primary psychotic illness lasting 1 to 6 months.

Antipsychotic Agents

The most simple and direct mechanism of action of antipsychotic agents involves blockade of postsynaptic dopamine receptors. Older agents are generally more potent dopamine blockers, with the high-potency neuroleptics (such as haloperidol) providing the most direct blockade and the low-potency agents (such as chlorpromazine) more associated with anticholinergic and antiadrenergic effects. The antipsychotic effects of these agents result from their actions on the dopaminergic neurons of the limbic system, midbrain tegmentum, septal nuclei, and mesocortical dopaminergic projections. Blockade of other dopaminergic pathways is responsible for adverse reactions: nigrostriatal (motor activity) blockade leads to extrapyramidal symptoms; tubuloinfundibular (pituitary and hypothalamus) blockade can increase prolactin levels and cause changes in temperature and appetite regulation. Because atypical antipsychotic agents have a less direct dopamine receptor blockade, they have a lower rate of extrapyramidal adverse reactions, although such reactions can still occur.

Adverse Reactions

Several types of adverse reactions to antipsychotic agents are common and important. Their relationship to specific antipsychotic agents is reviewed in Table 71.1.

Acute dystonic reactions occur within hours or days after treatment is initiated with antipsychotic drugs. Dystonia is an uncontrollable tightening of muscles, such as the sternocleidomastoid muscle (causing neck twisting, or torticollis), the extraocular muscles (oculogyric crisis), or the laryngeal muscles (respiratory difficulties). Treatment is with parenteral administration of an anticholinergic agent (eg, diphenhydramine).

Akathisia is an unpleasant feeling of restlessness and the inability to sit still, which generally occurs within days of the initiation or an increase of an antipsychotic dose. Akathisia is sometimes mistaken for exacerbation of psychosis. Treatment consists of a decrease in the dose of the antipsychotic agent (if possible) or use of a β-blocking agent such as propranolol.

Table 71.1 • Review of Antipsychotic Agents

Drugs	Toxic/Adverse Effects	Drug Interactions/Comments
Typical agents Chlorpromazine Fluphenazine Haloperidol Loxapine Mesoridazine Molindone Perphenazine Thioridazine Thiothixene Trifluoperazine	EPS—dystonia, parkinsonism, akathisia; TD, NMS (more with high-potency agents [eg, haloperidol]) Anticholinergic effects, sedation, orthostatic hypotension (more with low-potency agents [eg, chlorpromazine]) Galactorrhea, amenorrhea, gynecomastia, weight gain, sexual dysfunction Photosensitivity, risk of seizures Pigmentary retinopathy—thioridazine	Exercise caution for patients with QTc >450 ms and coadministration of other drugs that cause QTc prolongation Additive sedative effects with CNS depressants Decreased concentrations in presence of carbamazepine, barbiturates, cigarette smoking Increased concentrations in presence of quinidine, fluoxetine, paroxetine Antihypertensive agents may produce additive hypotensive effects Haloperidol and fluphenazine available as depot, long-acting injectables
Atypical agents[a] Aripiprazole Brexpiprazole Cariprazine Ziprasidone Asenapine Lurasidone Iloperidone Paliperidone Risperidone Quetiapine Olanzapine Clozapine	Increased risk of DM, weight gain, and elevated triglyceride levels—greatest with clozapine and olanzapine Increased mortality rate in patients with dementia who are treated for behavioral disorders Risk of EPS and elevated prolactin levels highest with risperidone and paliperidone (dose related) Anticholinergic effects greatest with clozapine and olanzapine Risk of orthostatic hypotension greatest with clozapine, risperidone, and quetiapine Sedative risks greatest with clozapine, olanzapine, and quetiapine Increased risk of seizures and myocarditis with clozapine (dose related) Mandatory WBC count monitoring with clozapine (risk of agranulocytosis)	Less risk of EPS, TD, and prolactin effects than with typical agents Lower levels of all agents when used concurrently with carbamazepine; additive orthostatic hypotension with trazodone Aripiprazole—unique mechanism with both dopamine antagonist and agonist activity Aripiprazole, risperidone—increased levels with paroxetine, fluoxetine, duloxetine Clozapine—increased risk of agranulocytosis with captopril, carbamazepine, sulfonamides Clozapine, olanzapine—increased levels with use of cimetidine, erythromycin, fluoroquinolones, fluoxetine, fluvoxamine; decreased levels with cigarette smoking Paliperidone—cytochrome P450 interactions unlikely Quetiapine—increased levels with ketoconazole and nefazodone; decreased levels with phenytoin Risperidone, paliperidone, aripiprazole, and olanzapine available as depot, long-acting injectables

Abbreviations: CNS, central nervous system; DM, diabetes mellitus; EPS, extrapyramidal symptoms; NMS, neuroleptic malignant syndrome; QTc, corrected QT interval; TD, tardive dyskinesia; WBC, white blood cell.

[a] Listed in approximate order of least weight gain to most weight gain.

KEY FACTS

- ✓ Clues to the cause of psychosis can often be found in the temporal relationships among illness, medication, and symptom onset
- ✓ Brief psychotic disorder and schizophreniform disorder both are primary psychotic illnesses, but the former lasts less than 1 month and the latter, 1 to 6 months
- ✓ Antipsychotic agents act most simply and directly by blocking postsynaptic dopamine receptors
- ✓ Acute dystonic reactions occur within hours or days after the start of antipsychotic drug therapy
- ✓ Akathisia generally occurs within days of the start or an increase of an antipsychotic dose

Neuroleptic malignant syndrome is a potentially life-threatening disorder that may occur after the use of any antipsychotic agent, although it is more common with rapid increases in the dosage of high-potency antipsychotic agents. It is characterized by rigidity, fever, leukocytosis, tachycardia, tachypnea, diaphoresis, blood pressure fluctuations, and a marked increase in creatine kinase levels because of muscle breakdown. Treatment consists of discontinuing the use of the antipsychotic and providing life-support measures (ventilation and cooling). Pharmacologic interventions include dantrolene, a direct-acting muscle relaxant, and bromocriptine, a centrally acting dopamine agonist. Electroconvulsive therapy is also effective.

Parkinsonian symptoms have a more gradual onset and can be treated with oral anticholinergic agents or a decreased dose of an antipsychotic agent, or both.

Tardive dyskinesia has an incidence of 3% to 5% annually with use of first-generation neuroleptics and consists of involuntary movements of the face, trunk, or extremities. The most consistent risk factors for its development are long-term medication use (>6 months) and older age. It is best when treatment with the antipsychotic agent can be discontinued at an early sign of tardive dyskinesia, because the dyskinesia is sometimes reversible. Tardive dyskinesia is rarer with atypical antipsychotics.

Glucose intolerance, weight gain, and *electrophysiologic cardiac changes* have been associated with atypical antipsychotics. Additionally, several studies have shown a lack of efficacy in off-label use of atypical antipsychotics for patients with dementia, and safety concerns have arisen related to an increased risk of death among these patients.

Clozapine adverse reactions include seizures, orthostasis, and myocarditis. This atypical antipsychotic also has a 1% to 2% risk of producing agranulocytosis, which is reversible if use of the medication is discontinued immediately. Because of this serious potential reaction, a specific requirement of clozapine use is regular white blood cell counts (weekly for the first 6 months).

Somatic Symptom and Related Disorders

The most meaningful change in the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) was in the area of somatic symptoms. Diagnoses of somatization disorder, hypochondriasis, pain disorder, and undifferentiated somatoform disorder have been removed, and many patients who received the formal diagnosis of one of those disorders may now be considered to have a somatic symptom disorder. The major conceptual change was a move to a descriptive focus that is less concerned with whether or not a medical cause is known and more concerned with the impact on functioning.

Somatic Symptom Disorder

Somatic symptom disorder involves somatic symptoms that are either highly distressing or markedly disrupt functioning, as well as excessive and disproportionate thoughts, feelings, and behaviors associated with these symptoms. The symptoms may or may not be medically explained. As an example, dizziness may result in a somatic symptom disorder whether or not its cause is known; the focus is on the impact of and reaction to the symptom.

Some patients with heart disease or cancer have a normal adjustment to their condition—perhaps some anxiety about medical tests, mild sleep disruption, and worries about their family and future. Others have a somatic symptom disorder, in which their concerns about their symptoms may make them unusually attuned to subtle somatic experiences, with associated thoughts (ruminative worry), feelings (such as terror), and behaviors (such as avoidance) that are clearly out of proportion to the somatic illness.

Many patients with somatic symptom disorder have multiple somatic symptoms, but some may have only 1 symptom, such as pain. Patients with somatic symptom disorder typically worry excessively and may misinterpret a physician's reassurance as not caring. Good practice, nonetheless, involves providing appropriate—neither excessive nor minimalist—testing for and treatment of medical illnesses. After a medical cause of symptoms has been ruled out, a repeat of testing is unnecessary and may fuel the patient's problems. Because patients with somatic symptom disorder may seek care from multiple providers, unifying their medical care with an increased coordination can be helpful.

Illness Anxiety Disorder

Illness anxiety disorder is a preoccupation with and fear of having or acquiring a serious disorder. Patients with illness anxiety may misinterpret body sensations such as borborygmi, heartbeats, or sweating. The disorder is diagnosed when a medical cause has been ruled out and the anxiety and functional impairment persist for more than 6 months despite appropriate medical evaluation and reassurance. Patients may either seek frequent care or avoid care in response to their illness anxiety.

Key Definition

Illness anxiety disorder: *a preoccupation with and fear of having or acquiring a serious disorder.*

Conversion Disorder (Functional Neurologic Symptom Disorder)

Conversion disorder is a loss or alteration of neurologic functioning suggestive of a disorder that cannot be explained on the basis of known physiologic mechanisms. It is seen most often in the outpatient setting. One example is loss of vision despite intact visual pathways. Patients often respond to any of several therapeutic modalities that suggest hope of a cure. When conversion disorder becomes chronic, it carries a poorer prognosis and is difficult to treat.

Factitious Disorders

Factitious disorders are characterized by the *deliberate* production of signs or symptoms of disease. The diagnosis of these disorders requires that the physician maintain a high degree of awareness and look for objective data at variance with the patient's history (eg, surgical scars that are inconsistent with past surgical history). The more common form of factitious disorder generally occurs among socially conforming young women of a higher socioeconomic class who are intelligent, educated, and often work in a medically related field. The possibility of a coexisting medical disorder or intercurrent illness needs to be appreciated in the diagnostic and therapeutic management of these difficult cases. Factitious disorders are often seen in patients with a history of childhood emotional traumas. The disorder may be imposed on oneself or on another (formerly called *by proxy*).

KEY FACTS

- ✓ Neuroleptic malignant syndrome can occur with any antipsychotic but is more likely to follow a rapid increase in dosage of high-potency agents
- ✓ Long-term antipsychotic use (>6 months) and older age increase the risk of tardive dyskinesia
- ✓ Somatic symptom disorder includes extremely distressing or disruptive somatic symptoms and associated excessive and disproportionate thoughts, feelings, and behaviors
- ✓ In factitious disorders, signs and symptoms are produced intentionally

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Substance Use Disorders, Personality Disorders, and Eating Disorders

BRIAN A. PALMER, MD; BHANUPRAKASH KOLLA, MD

Substance Use Disorders

Alcohol and other substance use disorders are a major concern in all age groups and across all ethnic, socioeconomic, and racial groups. Despite high lifetime prevalence (up to 20%), less than 10% of persons with substance use disorders are involved in treatment (either self-help groups or professional care).

Several pharmacologic agents are available to help diminish the craving for alcohol and other drugs or to deter relapse. Although some of the medications, including disulfiram, acamprosate, and naltrexone, may help prevent relapse, they are adjunctive and are not intended as a substitute for comprehensive psychosocial treatment.

A substance use disorder is diagnosed when a patient meets at least 2 of the following 11 criteria, listed in *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition), within the same 12 months (mild, 2 or 3 criteria; moderate, 4 or 5 criteria; severe, 6 or more criteria).

1. Use of more of the substance or use over a longer period than originally intended
2. Unsuccessful efforts to control use or worries about cutting down or stopping
3. Large amounts of time spent obtaining, using, or recovering from the substance
4. Breakdown in meeting obligations at home, work, or school
5. Giving up former interests
6. Craving the substance
7. Use of the substance despite mental or physical health consequences
8. Use of the substance despite relationship consequences
9. Recurrent use of the substance when the timing is dangerous (eg, while driving)
10. Development of **tolerance** (needing more of the substance for the same effect)
11. Withdrawal symptoms after use is stopped

Key Definition

Tolerance: *needing more of the substance for the same effect.*

Alcohol Use Disorders

A positive response to 2 or more of the questions of CAGE (related to attempts to *c*ut down on alcohol use, other persons expressing *a*nnoyance, experiencing *g*uilt, and *e*arly-morning drinking) has an excellent sensitivity and specificity for alcohol use disorders. Alcohol withdrawal can range from mild to severe, beginning with tachycardia, hypertension, diaphoresis, and tremors and progressing to withdrawal seizures or delirium tremens, or both.

Psychological functioning issues could include impaired cognition and changes in mood and behavior. Interpersonal functioning issues include marital problems, child abuse, and impaired social relationships. Occupational functioning issues include academic, scholastic, or job problems. Legal, financial, and spiritual problems also occur. In the long term, serious physical consequences could occur (eg, liver failure, cognitive impairment).

Benzodiazepine, Sedative-Hypnotic, and Anxiolytic Use Disorders

Benzodiazepines, sedative-hypnotics, and anxiolytics are widely prescribed in many areas of medicine, so abuse and dependence often have an iatrogenic component. The following 5 characteristics may help distinguish medical use from nonmedical use.

1. Intent: What is the purpose of the use?
2. Effect: What is the effect on the user's life?
3. Control: Is the use controlled by the user only, or does a physician share in the control?
4. Legality: Is the use of the drug legal or illegal? Medical drug use is legal.
5. Pattern: In what settings is the drug used?

Withdrawal from benzodiazepine and barbiturate use, in particular, may be serious because of the increased risk of withdrawal seizures. Slow tapering of doses is indicated, particularly following long-term use.

Opioid Use Disorder

Opioids are prescribed and abused at historically high rates despite the limited evidence as medical therapy for most chronic pain conditions. Heroin use also has been increasing steadily. Diversion is a common problem. Opioid withdrawal symptoms include diarrhea, dilated pupils, muscle aches or cramps, nausea, increased pulse rate and blood pressure, and piloerection (gooseflesh). Opioid overdoses can result in respiratory suppression and death.

Personality Disorders

The 10 personality disorders described in the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) are grouped into 3 clusters (Boxes 72.1 through 72.3).

Patients with borderline personality disorder (BPD) and other Cluster B disorders (antisocial, narcissistic, and histrionic disorders) demand the most from internists. BPD is diagnosed with 9 criteria that are categorized as interpersonal (eg, chaotic relationships, ideal and devalued; efforts to avoid abandonment), affective (eg, lability, anger problems), self (eg, identity confusion, emptiness), and behavioral (eg, suicide attempts, self-injury, impulsivity). The disorder is treatable and generally improves despite common perceptions to the contrary. Internists can be most effective by practicing medicine within appropriate standards of care (holding limits where necessary), clarifying the patient's experience, and working together in teams.

Eating Disorders

The 2 common eating disorders are anorexia nervosa and bulimia. Both are markedly more prevalent among women than men. Onset is usually in the teenage or young adult years. Eating disorders are increasingly found across all income, racial, and ethnic groups. Both disorders have a primary symptom of preoccupation with weight and distortion of body image. For example, the patient perceives that she looks less attractive and looks overweight in contrast to an observer's perception. The disorders are not mutually exclusive, and about 50% of patients with anorexia nervosa also have bulimia. Many patients with bulimia have had at least a subclinical case of anorexia nervosa previously. Eating disorders have the highest lethality of all psychiatric illnesses.

Box 72.1 • Personality Disorders, Cluster A (Odd or Eccentric Character Structure)

- Paranoid personality
  - Distrust and suspiciousness, assumption of malevolent motives
- Schizoid personality
  - Social detachment, restricted affect socially, no need or want for social connection
- Schizotypal personality
  - Interpersonal deficits, difficulties with closeness, cognitive and perceptual disturbances (schizophrenia spectrum), behavioral eccentricities

From Oldham JM. Personality disorders: current perspectives. JAMA. 1994 Dec 14;272(22):1770-6; used with permission.

Anorexia Nervosa

To meet the diagnostic criteria of anorexia nervosa, weight must be 15% below that expected for age and height. However, a weight 30% to 40% below normal is not uncommon and can lead to the medical complications of starvation,

Box 72.2 • Personality Disorders, Cluster B (Dramatic, Emotional, or Erratic Character Structure)

- Antisocial personality
  - Diagnosed in adults who had conduct disorder before age 15 y, pervasive disregard for and violation of the rights of other persons
- Borderline personality
  - Instability of interpersonal relationships, self-image, and affect; marked impulsivity
- Histrionic personality
  - Excessive emotionality and attention-seeking
- Narcissistic personality
  - Grandiosity (fantasy or behavior), need for admiration, lack of empathy

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Box 72.3 • Personality Disorders, Cluster C (Anxious or Fearful Character Structure)

Avoidant personality
  Social inhibition, feelings of inadequacy, hypersensitivity to negative appraisal
Dependent personality
  Excessive need to be cared for; submissive or clinging behavior, separation fear
Obsessive-compulsive personality
  Orderliness, perfectionism, mental or interpersonal control; inflexibility, lack of openness

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such as depletion of fat, muscle wasting, bradycardia, arrhythmias, ventricular tachycardia and sudden death, constipation, abdominal pain, leukopenia, hypercortisolemia, and osteoporosis. Extreme cases are characterized by lanugo (fine hair on the body) and metabolic alterations to conserve energy. Thyroid effects include low levels of triiodothyronine (T_3), cold intolerance, and difficulty maintaining core body temperature. Reproductive effects include a pronounced decrease in or cessation of the secretion of luteinizing hormone and follicle-stimulating hormone, often resulting in secondary amenorrhea. Reinitiation of nourishment requires careful monitoring and supplementation of potassium, magnesium, and phosphate levels to avoid refeeding syndrome. Patients could present with episodes of severe food restriction (the restricting type) or alternately have episodes of binge eating followed by purging (the binge eating–purging type).

Bulimia

Patients with bulimia often consume large quantities of food followed by purging. Physical complications of the binge-purge cycle may include fluid and electrolyte abnormalities, hypochloremic-hypokalemic metabolic alkalosis, esophageal and gastric irritation and bleeding, colonic abnormalities from laxative abuse, marked erosion of dental enamel with associated decay, parotid and salivary gland hypertrophy, and amylase levels 25% to 40% higher than the reference range. If bulimia is untreated, it often becomes chronic. Some patients have a gradual spontaneous remission of some symptoms.

KEY FACTS

- ✓ Available therapies for substance use disorders include pharmacologic agents to help diminish cravings and deter relapse
- ✓ The CAGE questions—a helpful diagnostic tool for alcohol use disorders, with excellent sensitivity and specificity
- ✓ Symptoms of alcohol withdrawal—can range from mild to severe
- ✓ For the diagnosis of anorexia nervosa, patients must weigh at least 15% less than normal for their age and height
- ✓ The binge-purge cycle of bulimia may cause various physical complications, from fluid and electrolyte abnormalities to erosion of dental enamel

XI Questions and Answers

Questions

Multiple Choice (Choose the best answer)

XI.1. A 27-year-old woman presents for an evaluation. She reports sudden bouts of anxiety that occur out of the blue. They last for about 5 to 10 minutes and resolve on their own. During these episodes, she notes substantial palpitations, tremors, difficulty breathing, and an impending sense of doom. In addition, she notes an irrational fear of being in places from which she cannot quickly extricate herself. What is the most likely diagnosis in this patient?

a. Panic disorder
b. Agoraphobia
c. Generalized anxiety disorder
d. Panic disorder with agoraphobia

XI.2. A 59-year-old man with a diagnosis of major depressive disorder is currently being treated with an antidepressant. He presents with concerns of urinary retention, dry mouth, and lightheadedness. The antidepressant that he most likely is taking is which of the following?

a. Fluoxetine
b. Mirtazapine
c. Nortriptyline
d. Citalopram

XI.3. A 45-year-old woman notes that she has to repeatedly wash her hands to rid herself of a fear of unclean hands that will spread disease. If she does not do this washing, she has pronounced anxiety. The most appropriate behavior management for this patient's disorder is which of the following?

a. Relaxation training
b. Diaphragmatic breathing
c. Exposure and response prevention
d. Avoidance therapy

XI.4. A 53-year-old woman presents with reports of considerable anxiety following a myocardial infarction, which occurred about 2 years ago. She describes substantial anxiety about any chest discomfort and has concern about her heart health despite being reassured that her most recent coronary angiogram did not show any abnormalities. She spends an excessive amount of time researching her condition and ways to mitigate her risk. Her husband describes a substantial deterioration in her functioning secondary to the amount of time she spends worried and anxious about her condition. Her psychiatric diagnosis is most likely which of the following?

a. Somatic symptom disorder
b. No current psychiatric disorder
c. Illness anxiety disorder
d. Conversion disorder

XI.5. After a complete medical and psychiatric evaluation, a 55-year-old woman receives the diagnosis of somatic syndrome disorder. She has been seeking care from multiple health care providers and has had multiple repeat investigations. The best first step in her care should include which of the following?

a. Initiation of antipsychotic therapy
b. Initiation of β-blocker therapy
c. Initiation of antidepressant therapy
d. Increased coordination of care

XI.6. A 24-year-old man recently received the diagnosis of schizophreniform disorder. His therapy was started with risperidone. Within 3 days of taking the medication, the patient reported that he felt unwell. On examination, he appeared febrile with a temperature of 39°C. He had extensive muscle rigidity and appeared confused and disoriented. Laboratory investigations showed an increased white blood cell count and elevated creatine kinase level. What is the most likely diagnosis in this patient?

a. Tardive dyskinesia
b. Neuroleptic malignant syndrome
c. Acute dystonia
d. Malingering

XI.7. A 17-year-old female dancer presents for an evaluation of her osteoporosis. On examination, she appears to be severely underweight with a body mass index of 15 kg/m^2. She describes not having regular periods. On further questioning, she notes eating very small meals at infrequent intervals. She considers herself to be overweight. What is the most likely diagnosis in this patient?

a. Borderline personality disorder
b. Bulimia nervosa
c. Anorexia nervosa, binge eating–purging type
d. Anorexia nervosa, restricting type

XI.8. A 22-year-old woman presents to the emergency department following an impulsive suicide attempt. She describes a history of difficult relationships with multiple partners. She notes a chronic low mood that is associated with a feeling of emptiness, difficulty controlling her temper, and feelings of intense happiness and sadness. The most likely diagnosis of her condition is which of the following?

a. Borderline personality disorder
b. Schizoid personality disorder
c. Narcissistic personality disorder
d. Antisocial personality disorder

Answers

XI.1. Answer d.

The patient reports panic disorder, along with episodes of sudden anxiety and a fear of being in places that she cannot leave quickly. This report suggests a diagnosis of both panic disorder and agoraphobia. Panic disorder, agoraphobia, and generalized anxiety disorder independently would not be correct diagnoses in this patient because of the presence of the 2 disorders simultaneously.

XI.2. Answer c.

The patient is having anticholinergic adverse effects and orthostatic hypotension. These symptoms are most likely to result from tricyclic antidepressants such as nortriptyline. Selective serotonin reuptake inhibitors and mirtazapine are unlikely to cause them.

XI.3. Answer c.

On the basis of her described symptoms, this patient has obsessive-compulsive disorder. The most evidence-based treatment of this condition is exposure and response prevention. Relaxation training and diaphragmatic breathing would not treat the root of the problem. Avoidance is likely to make the condition worse.

XI.4. Answer a.

Despite a medical diagnosis, the patient shows anxiety and functional impairment that are out of proportion to her medical problem. These have resulted in substantial overall impairment. Her symptoms indicate a diagnosis of somatic symptom disorder. She does not describe irrational worry about a particular diagnosis that would indicate illness anxiety disorder. She does not note unexplained neurologic impairment that would indicate a conversion disorder.

XI.5. Answer d.

The most appropriate first step in the management of somatic syndrome disorder is increased coordination of care among the various health care providers. Repeat testing is usually unnecessary and might result in the patient's further deterioration. Antipsychotic and β-blocker medications are not indicated for this condition. If the patient has symptoms suggestive of major depressive disorder, therapy with an antidepressant could be initiated.

XI.6. Answer b.

Neuroleptic malignant syndrome can be life threatening and should be identified immediately. This condition occurs after initiation of an antipsychotic medication and results in fever, muscle rigidity, an elevated creatine kinase level, leukocytosis, and blood pressure fluctuations. Immediately, the offending medication should be discontinued and life support care provided.

XI.7. Answer d.

This patient has seriously low weight and has consequences secondary to her low weight, including osteoporosis and secondary amenorrhea. She has a distorted perception of her weight. She does not describe overeating and purging. She notes severe caloric restriction, which is suggestive of anorexia nervosa, restricting type.

XI.8. Answer a.

The patient meets criteria for borderline personality disorder with reports of impulsivity, suicidal gestures, difficult interpersonal relationships, feelings of emptiness, and emotional lability.

Section

XII

Pulmonology

73

Critical Care Medicine

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Respiratory Critical Care

Effective functioning of the respiratory system requires 1) normal central nervous system control, 2) intact neuromuscular transmission and bellows function, 3) patent airways, and 4) normal gas exchange at the alveolar-capillary level. Respiratory failure may be caused by dysfunction at any of these levels, resulting in failure of oxygenation (*hypoxemic respiratory failure*) or ventilation (*hypercapnic respiratory failure*).

Hypoxemic Respiratory Failure

Hypoxemic respiratory failure is typically defined as an arterial oxygen tension of less than 60 mm Hg. The cause of hypoxemic respiratory failure can be further delineated by patient history and by calculation of the alveolar-arterial (A-a) gradient. The A-a gradient reflects the difference between the alveolar and arterial concentrations of oxygen and is calculated as follows:

$$\text{A-a Gradient} = \left[\mathrm{F{\small IO}}_2 \times \left(\mathrm{P{\small ATM}} - \mathrm{P{\small H}}_2\mathrm{O}\right) - (\mathrm{Pa{\small CO}}_2 / 0.8)\right] - \mathrm{Pa{\small O}}_2,$$

where FIO_2 is the fraction of inspired oxygen, $\mathrm{P_{ATM}}$ is sea level atmospheric pressure (760 mm Hg), and $\mathrm{PH_2O}$ is the partial pressure of water vapor (47 mm Hg). Normally, the A-a gradient is less than 10 mm Hg in a young adult; it increases by 10 mm Hg every decade thereafter.

Key Definition

Hypoxemic respiratory failure: *arterial oxygen tension <60 mm Hg.*

Hypoxemia may result from processes with either a normal or an abnormal A-a gradient. Hypoxemia with a normal A-a gradient can be caused by a decrease in the inspired PO_2 (eg, altitude) or hypoventilation (eg, narcotic use). Hypoxemia with an abnormal A-a gradient can be caused by decreased diffusion (eg, idiopathic pulmonary fibrosis), ventilation-perfusion ratio ($\dot{V}/\dot{Q}$) mismatch, or shunt. $\dot{V}/\dot{Q}$ mismatch occurs with inadequate ventilation or inadequate perfusion (eg, chronic obstructive pulmonary disease [COPD]) and responds to supplemental oxygen. Shunting occurs when alveoli are bypassed—called an anatomical shunt (eg, an intracardiac shunt)—or when nonventilated lung is perfused—called a physiologic shunt (eg, as in acute respiratory distress syndrome [ARDS]). A shunt typically does not respond to supplemental oxygen, but a physiologic shunt often responds to recruitment of nonventilated alveoli with positive end-expiratory pressure (PEEP).

Hypercapnic Respiratory Failure

Hypercapnic respiratory failure is caused by inadequate alveolar ventilation that is generally the result of airway obstruction, increased dead space ventilation, or decreased minute ventilation (decreased rate, depth, or drive of breathing) compared with demand (eg, overdose or neuromuscular weakness). **Physiologic dead space** is the portion of a breath that is not involved in gas exchange (ie, in the hypopharynx, trachea, and conducting airways). The amount of dead space increases with several disease states (eg, COPD).

Key Definition

Physiologic dead space: *the portion of a breath that is not involved in gas exchange (ie, in the hypopharynx, trachea, and conducting airways).*

Management of Respiratory Failure

Noninvasive Ventilation

Continuous positive airway pressure (CPAP) machines help alleviate obstruction in obstructive sleep apnea and relieve pulmonary edema and hypoxia in congestive heart failure. Noninvasive ventilation with a bilevel positive airway pressure machine allows for positive pressure ventilation without endotracheal intubation. The typical indication is treatment of hypercapnic respiratory failure in COPD exacerbation. Contraindications to noninvasive ventilation include high aspiration risk, copious secretions, facial trauma, unstable airway patency, and cardiac or respiratory arrest.

Failure of Airway Patency

Failure of airway patency can occur in cases of obstruction or loss of normal gag and cough reflexes (eg, in a person with a decreased mental status). Patients who have lost airway patency or who could lose it (eg, burn victims with inhalation injury) should undergo endotracheal intubation for airway protection.

Endotracheal Intubation

Endotracheal intubation allows maximal control of the airway, enables delivery of specific inspired oxygen concentrations and positive pressure ventilation, and provides protection from aspiration. Indications for intubation include loss of airway patency or threat of loss, sedation with loss of normal control of ventilation, and respiratory failure requiring mechanical ventilation. Complications of intubation include vomiting and aspiration, hypoxemia or hypotension during the procedure, inadvertent intubation of the esophagus, complications from administered medications (eg, succinylcholine causing hyperkalemia), or an intubation attempt leading to an inability to intubate or ventilate (ie, failed airway management).

Mechanical Ventilation

Patients who require mechanical ventilation usually meet the criteria for ventilator support (Table 73.1). The goals of mechanical ventilation are to 1) correct hypoxia, 2) support or improve ventilation, 3) decrease the work of breathing, and 4) support lung injury healing.

Setting the Ventilator

Oxygen Delivery

Oxygen flow is typically set at the lowest $\mathrm{FIO_2}$ that will keep the oxygen saturation at about 90%. Too much oxygen can lead to damage due to oxygen toxicity.

Rate of Ventilation

The respiratory rate multiplied by the tidal volume (V_T) is the *minute ventilation*. If a patient is hypercapnic, an increase in minute ventilation is necessary to correct the problem. Increases in the set respiratory rate can lead to insufficient time to exhale the full breath before initiation of the next breath (typically when the respiratory rate exceeds 30-35 breaths/min, but it can occur at lower rates in obstructive lung disease). This can lead to increased intrathoracic pressure (called intrinsic PEEP or auto-PEEP) and hemodynamic instability. Conversely, increasing the V_T can lead to volutrauma, especially in lung injury; typically, the ideal V_T is 6 mL/kg ideal body weight in diagnoses such as ARDS. If neither respiratory rate nor V_T can be safely increased, clinicians sometimes tolerate hypercapnia, especially if it is mild (termed *permissive hypercapnia*).

Table 73.1 • Typical Physiologic Criteria for Mechanical Ventilator Support

Variable	Value
Respiratory rate, breaths/min	>25-30
Minute ventilation, L/min	>10-15
Maximal inspiratory pressure (force), cm H_2O	<20
Vital capacity, mL/kg	<10
$\mathrm{PaO_2}$, mm Hg	<60 with $\mathrm{FIO_2}$>0.60
$\mathrm{PaO_2/FIO_2}$	<200
$\mathrm{PAO_2 - PaO_2}$, mm Hg	>300 with $\mathrm{FIO_2}$=1.00
V_{DS}/V_T	>0.60
pH	<7.20 (with a predominant respiratory component)

Abbreviations: $\mathrm{FIO_2}$, fraction of inspired oxygen; $\mathrm{PAO_2 - PaO_2}$, alveolar-arterial gradient in partial pressure of oxygen; V_{DS}, dead space volume; V_T tidal volume.

Positive End-Expiratory Pressure

PEEP is intended to increase functional residual capacity, recruit partially collapsed alveoli, improve lung compliance, and improve $\dot{V}/\dot{Q}$ matching. It decreases atelectrauma (recruitment and derecruitment of alveoli). An adverse effect of PEEP is an excessive increase in intrathoracic pressure with decreased cardiac output. Overdistention of lung units may also worsen gas exchange because of ventilator-induced lung injury. At levels of PEEP greater than 10 to 15 cm H_2O, barotrauma is a concern. The optimal PEEP may be defined as the lowest level of PEEP needed to achieve satisfactory oxygen delivery at a nontoxic $\mathrm{FIO_2}$ (<0.60).

Mode of Ventilation

The presence or absence of a set ventilator rate, the control (or set upper limit) of either the pressure or the V_T, and the percentage of machine-controlled breaths determine the *mode* of ventilation (Table 73.2). Patients can have all their breaths predetermined (assist-control mode), some of their breaths predetermined (synchronized intermittent mandatory ventilation mode), or none of their breaths predetermined (spontaneous mode).

Table 73.2 • Basic Ventilator Modes and Settings

Mode	Description or Mechanism
	Volume Control Modes
AC, also called CMV	Active inhalation VT is delivered up to a volume threshold and not a pressure threshold Exhalation is passive; after the VT is delivered, the machine releases and exhalation is driven by chest wall and lung elastance (recoil) Patient initiates the respiratory cycle (unless apneic or paralyzed) Machine senses inspiratory effort and then delivers machine-defined VT for every breath Does not allow patient to breathe spontaneously (ie, patient-defined VT) Machine rate (eg, CMV = 8 breaths/min) defines the minimum number of VT breaths per minute that a patient will receive A patient who initiates more breaths per minute than the defined rate will receive those breaths at the machine-defined VT
SIMV	Active inhalation VT is delivered up to a volume threshold and not a pressure threshold Exhalation is passive; after the VT is delivered, the machine releases and exhalation is driven by chest wall and lung elastance (recoil) Patient initiates the respiratory cycle (unless apneic or paralyzed) Machine senses inspiratory effort and then delivers machine-defined VT for only the rate of machine breaths Machine rate (eg, SIMV=8 breaths/min) defines the actual number of VT breaths per minute that a patient will receive A patient who initiates more breaths per minute than the defined rate will receive those breaths at the patient-defined VT (ie, the VT of the spontaneous breaths can be different from the VT of the machine breaths)
	Pressure Control Modes
PCV	Can be used with either CMV or SIMV modes Active inhalation VT is delivered up to a pressure threshold and not a volume threshold Exhalation is passive; after the VT is delivered, the machine releases and exhalation is driven by chest wall and lung elastance (recoil) Patient initiates the respiratory cycle (unless apneic or paralyzed)
	Additional Support Modes
CPAP	This is a spontaneous breathing mode (ie, VT and rate are not provided by the mechanical ventilator) Continuous positive pressure is delivered while a patient breathes spontaneously This pressure is continuous, meaning that both inspiratory and expiratory phases of respiration are supplemented with positive pressure CPAP may be delivered invasively (ie, through an endotracheal tube) or noninvasively (ie, with a tightly fitting mask or with high–gas flow nasal prongs)
PSV	PSV augments spontaneous breaths with a machine-defined amount of positive pressure that is delivered only during inspiration The purpose of PSV mode is to improve patient-machine synchrony (comfort) and to decrease the patient work of breathing; in some patients, this may facilitate weaning from mechanical ventilation PSV inspiratory positive flow continues while the patient inhales and then stops when the patient's flow decreases to less than a threshold value (usually <25% of the initial inspiratory flow rate) Patients determine their spontaneous VT during PSV breaths by controlling their flow rate. When they have had enough, they simply stop inspiring
	Initial Invasive Mechanical Ventilation Settings
Mode	As indicated: CMV, SIMV, PSV, CPAP
VT	Standard: approximately 8 mL/kg ideal body weight ARDS: 6 mL/kg ideal body weight
Rate	Titrate to desired VM for Pco2, PEEP, and TI
FIO$_2$	Maintain PO$_2$ higher than target value (usually 60 mm Hg)
TI	Set to meet patient demand Allow adequate time for exhalation
PEEP	As indicated; maintain lower values unless needed for ARDS Do not use as a prevention maneuver for atelectasis

Abbreviations: AC, assist-control; ARDS, acute respiratory distress syndrome; CMV, controlled mechanical ventilation; CPAP, continuous positive airway pressure; FIO$_2$, fraction of inspired oxygen; PCV, pressure control ventilation; PEEP, positive end-expiratory pressure; PSV, pressure support ventilation; SIMV, synchronized intermittent mandatory ventilation; TI, inspiratory time; VM, minute ventilation; VT, tidal volume.

In *assist-control mode*, the physician controls all breaths and chooses between either a preset volume (ie, volume-controlled ventilation) or a preset pressure limit (ie, pressure-controlled ventilation). In *pressure support mode* (also called CPAP mode), the patient determines the rate of breathing; however, the physician can adjust the amount of pressure support from the ventilator to increase the depth or size of breath or to decrease the work of breathing. This mode is typically used during weaning. In *intermittent mandatory ventilation mode*, the patient must take a physician-determined, preset number of breaths with preset parameters such as a fixed volume. Between these preset breaths, the patient may breathe spontaneously, typically with a set pressure to decrease the work of breathing.

KEY FACTS

✓ Requirements for effective respiratory system—
- normal central nervous system control
- intact neuromuscular transmission and bellows function
- patent airways
- normal gas exchange at the alveolar-capillary level

✓ Causes of hypercapnic respiratory failure (from inadequate alveolar ventilation)—
- airway obstruction
- increased dead space ventilation
- decreased minute ventilation compared with demand

✓ CPAP machine—
- relieves obstruction in obstructive sleep apnea
- relieves pulmonary edema and hypoxia in congestive heart failure

✓ Indications for intubation—
- loss of airway patency (or threat of loss)
- sedation with loss of normal control of ventilation
- respiratory failure requiring mechanical ventilation

✓ Minute Ventilation = Respiratory Rate × V_T

✓ PEEP—
- increases functional residual capacity
- recruits partially collapsed alveoli
- improves lung compliance
- improves $\dot{V}/\dot{Q}$ matching

Mechanical Ventilation Concerns

Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) is a serious, potentially preventable complication of mechanical ventilation. Mortality can be decreased with the use of a VAP bundle for VAP prevention, as recommended by the Institute for Healthcare Improvement (IHI) (Box 73.1).

Intrinsic PEEP

Intrinsic PEEP (also called auto-PEEP) is an important complication of positive pressure ventilation. Inadequate time during the expiratory phase of the respiratory cycle results in a new machine breath being delivered before the previous breath is completely exhaled. This may worsen hyperinflation, increase intrathoracic pressure, reduce venous return, and worsen associated complications (eg, barotrauma). Intrinsic PEEP may occur in spontaneously breathing patients with obstructive airway disease, but the effect is most important in mechanically ventilated patients. Immediate intervention in a ventilated patient with hemodynamic instability due to intrinsic PEEP includes temporary disconnection of the ventilator circuit to allow the patient to exhale and thus correct the hyperinflation. Subsequent treatment typically involves optimizing bronchodilator therapy and altering the ventilator cycle to allow optimal expiratory time.

Prolonged Intubation and Tracheostomy

Prolonged invasive mechanical ventilation increases the risk of tracheal injury and stenosis, bleeding, tracheoesophageal fistula, and, possibly, increased bronchial or pulmonary infections. For patients who require prolonged mechanical ventilation or airway support, the timing of tracheostomy is controversial. Tracheostomy is commonly considered for patients who have needed or are expected to need intubation and mechanical ventilation for more than 2 to 4 weeks. Tracheostomy has the advantages of decreased laryngeal injury, increased patient comfort, ease of suctioning, and, in certain patients, allowance for oral ingestion and speech.

Endotracheal Tube Problems

Ventilators can measure peak pressures and plateau pressures, and both should be monitored carefully. A high peak pressure

Box 73.1 • IHI Ventilator Bundle

Elevation of the head of the bed (to 30°)
Daily cessation of sedation and assessment of readiness for extubation
Peptic ulcer disease prophylaxis
Deep vein thrombosis prophylaxis
Daily oral care with chlorhexidine

Abbreviation: IHI, Institute for Healthcare Improvement.

alarm in the absence of a high plateau pressure often indicates a problem in the endotracheal tube (eg, mucous plugging, kinking of the tube, or biting of the tube).

The plateau pressure should be maintained at less than 30 cm H_2O to avoid barotrauma. An elevated plateau pressure can reflect abdominal distention (eg, abdominal compartment syndrome) or poor lung compliance (eg, pneumothorax, pneumonia, or pulmonary edema). The underlying cause should be treated (eg, surgery for abdominal compartment syndrome or decompression for pneumothorax). If worsening lung compliance due to underlying lung parenchymal process is the problem, the ventilator settings should be adjusted to decrease the plateau pressure (eg, decrease tidal volume).

Weaning From Mechanical Ventilation

Patients are candidates for weaning (ie, liberation) from mechanical ventilation when they are hemodynamically stable, the underlying pathophysiologic processes (both pulmonary and nonpulmonary) are resolving, and they have adequately recovered from respiratory failure. The most effective and consistent way to wean patients is to use a protocol that involves a nurse or respiratory therapist. Patients receiving mechanical ventilation should have a daily interruption of sedation with a spontaneous breathing trial. This can be done by disconnecting the patient from the ventilator circuit (a T-piece system) or by reducing support to spontaneous mode with a low-pressure support setting (typically, 5 cm H_2O) for 30 minutes to 2 hours. A weaning protocol is presented in Figure 73.1.

Acute Respiratory Distress Syndrome

ARDS is diffuse lung injury that causes acute hypoxic respiratory failure (in <1 week) with bilateral opacities that are not otherwise explained and respiratory failure that is not caused by cardiac failure or volume overload. When PEEP is set at 5 cm H_2O or more, ARDS is described as *mild* (Pao$_2$:Fio$_2$ ratio >200 cm H_2O but ≤300 cm H_2O), *moderate* (Pao$_2$:Fio$_2$ ratio >100 cm H_2O but ≤200 cm H_2O), or *severe* (Pao$_2$:Fio$_2$ ratio ≤100 cm H_2O). Mortality from ARDS has averaged about 43%, but recent studies suggest that the mortality rate is decreasing. Several conditions are associated with ARDS (Table 73.3).

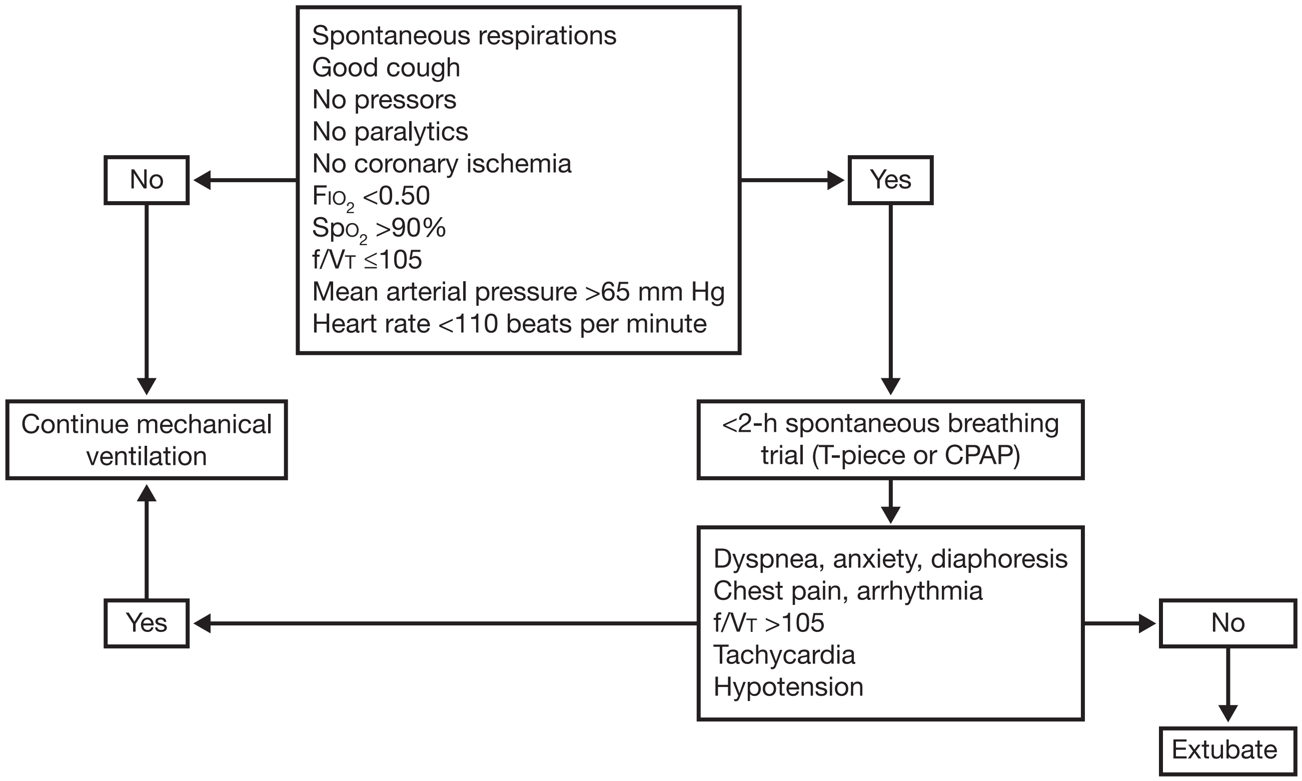
Spontaneous respirations
Good cough
No pressors
No paralytics
No coronary ischemia
Fio$_2$ <0.50
Spo$_2$ >90%
f/Vt ≤105
Mean arterial pressure >65 mm Hg
Heart rate <110 beats per minute
No
Yes
Continue mechanical ventilation
<2-h spontaneous breathing trial (T-piece or CPAP)
Dyspnea, anxiety, diaphoresis
Chest pain, arrhythmia
f/Vt >105
Tachycardia
Hypotension
Yes
No
Extubate

Figure 73.1. *Ventilatory Weaning Protocol. CPAP indicates continuous positive airway pressure; Fio$_2$, fraction of inspired oxygen; f/Vt, respiratory frequency divided by tidal volume (rapid shallow breathing index); Spo$_2$, arterial oxygen saturation.*

Key Definition

Acute respiratory distress syndrome: *acute (<1 week), diffuse lung injury that causes hypoxic respiratory failure that is not caused by cardiac failure or volume overload and is accompanied by bilateral opacities that are otherwise unexplained.*

Treatment involves mechanical ventilation strategies (ie, lung-protective ventilatory strategies) that allow for lung healing. These strategies include maintaining a tidal volume of 6 mL/kg (based on ideal body weight) and maintaining plateau airway pressures at less than 30 cm H_2O. Because ARDS patients have a physiologic shunt, hypoxemia is treated with incremental PEEP levels to increase and maintain alveolar recruitment and prevent alveolar derecruitment. In addition, prone positioning has been used to open flooded dependent alveoli and improve $\dot{V}/\dot{Q}$ matching and oxygenation, with a resultant improvement in mortality. Evidence also supports the use of paralytic medication for 48 hours in patients with severe ARDS, although with concerns of critical illness polyneuropathy, practitioners may be more selective with implementation. A conservative fluid strategy to maintain adequate systemic perfusion is preferred. Throughout the course of critical illness, acute and chronic supplemental nutrition (enteral feeding) is recommended if tolerated. Patient mobilization with ambulation and weaning from the ventilator are also initiated as soon as possible for all patients with ARDS.

Table 73.3 • Conditions Associated With Acute Respiratory Distress Syndrome (ARDS)[a]

Disorder or Type of Disorder	Cause
Shock	Any cause
Sepsis	Lung infections, other bacteremic or endotoxic states
Trauma	Head injury, lung contusion, fat embolism
Aspiration	Gastric, near-drowning, tube feedings
Hematologic	*Transfusions*, leukoagglutinin, *disseminated intravascular coagulation*, thrombotic thrombocytopenic purpura
Metabolic	Pancreatitis, uremia
Drug-related	Narcotics, barbiturates, aspirin
Toxic	Inhaled—oxygen, smoke Chemicals—paraquat Irritant gases—nitrogen dioxide, chlorine, sulfur dioxide, ammonia
Miscellaneous	Radiation, air embolism, high altitude

[a] Terms in italics indicate disorders and causes most commonly associated with ARDS.

The use of corticosteroids in the early stages of ARDS is controversial. If ARDS is caused by a steroid-responsive process, glucocorticoids are administered. Nitric oxide and other vasodilating agents provide short-term improvement in oxygenation but no mortality benefit for patients with ARDS. High-frequency oscillator ventilators were not effective in reducing mortality in clinical trials. Data are emerging on the use of extracorporeal membrane oxygenation (ECMO) in patients with ARDS; however, consensus has not been reached on its application.

If acute lung injury develops in a patient within 6 hours after receiving a blood product, the patient may have transfusion-related acute lung injury (TRALI) or TRALI/transfusion ARDS. Patients with TRALI present with noncardiogenic pulmonary edema, resultant pulmonary infiltrates, and hypoxia. TRALI is thought to be caused by an endothelial injury with resultant neutrophilic activation. Treatment is supportive. Administration of more blood products from the same donor should be avoided. TRALI should be differentiated from transfusion-associated circulatory overload, which is pulmonary edema due to an excess volume of administered blood products.

Shock

Shock is defined as the inadequate provision of oxygen and metabolic substrate to the tissues. Oxygen delivery is expressed as the product of cardiac output and arterial oxygen concentration:

$$\text{Do}_2 = \text{CO} \times [(\text{Hb} \times 1.39 \times \text{Sao}_2) + (\text{Pao}_2 \times 0.003)],$$

where Do_2 is delivery of oxygen, CO is cardiac output, Hb is hemoglobin, Sao_2 is arterial saturation of hemoglobin with oxygen, and Pao_2 is arterial oxygen tension. Early recognition and treatment of hypoperfusion can decrease the ensuing inflammatory response to shock. Shock should be recognized as a state of hypoperfusion usually associated with hypotension. Signs of shock include tachycardia, tachypnea, hypotension, oliguria, altered mental status, metabolic acidosis, and abnormal renal or liver function.

Key Definition

Shock: *inadequate provision of oxygen and metabolic substrate to tissues.*

Initial assessment is aimed at determining the cause of shock. The following classification system is widely used: 1) hypovolemic (eg, hemorrhage), 2) distributive (eg, anaphylaxis), 3) cardiogenic (eg, myocardial infarction), and 4) obstructive (eg, cardiac tamponade) (Table 73.4).

Table 73.4 • Classification of Shock[a]

Shock Type	Preload (Central Venous Pressure)	Wedge Pressure	Systemic Vascular Resistance	Cardiac Output	Examples of Causes
Hypovolemic	↓	↓	↑	↓	Bleeding Vomiting, diarrhea Diuretic use (excess) Burns, exudative skin lesions Diabetes insipidus
Distributive	↔	↔	↓	↑	Sepsis Liver disease Anaphylaxis Thiamine deficiency Spinal cord injury (neurogenic shock)
Cardiogenic	↑ or ↔	↑	↑	↓	Pump failure (right- or left-sided) Acute coronary syndrome Acute mitral regurgitation
Obstructive	↔	↔	↔	↔	Cardiac tamponade (equalization of pressures)

[a] Arrows indicate increased (↑), decreased (↓), or no change (↔).

Hemodynamic Assessment

The use of pulmonary arterial catheters in critically ill patients has decreased since a landmark study showed that the harm exceeded the benefits.

Central Line Placement

The indications for central venous access are lack of adequate peripheral veins, need for medications or solutions that are hypertonic or phlebitic, need for long-term access, need for measuring central pressures, and access for procedures (hemodialysis and cardiac pacing). If a large volume of fluid is required for resuscitation, a short, large-bore catheter should be used because small-bore and long catheters slow the rate of resuscitation. The most common locations for central access are the internal jugular, subclavian, and femoral veins. Intraosseous devices are being used increasingly as an alternative for quick, temporary, emergent central access. Relative contraindications include the practitioner's procedural inexperience or inability to identify landmarks; the presence of coagulopathy (noncompressible sites, such as the subclavian vein, should be avoided), or infection or burn at the entry site; and thrombosis of the proposed central venous site. Direct ultrasonographic visualization improves the speed of placement and decreases the rate of complications. Complications of central venous catheterization include bloodstream infections, cardiac arrhythmias, pneumothorax, air embolism, vascular injury, catheter or guidewire embolism, catheter knotting, bleeding, and other potential complications of needle or catheter misplacement.

The IHI has identified prevention of catheter-related bloodstream infections (CR-BSIs) with use of the IHI Central Line Bundle as a key element in improving patient outcomes and preventing morbidity. The key components of the Central Line Bundle are 1) hand hygiene; 2) maximal barrier precautions upon insertion; 3) chlorhexidine skin antisepsis; 4) optimal catheter site selection, with avoidance of the femoral vein for central venous access in adult patients; and 5) daily review of line necessity, with prompt removal of unnecessary lines. Small, chlorhexidine-impregnated circular sponges can be placed at the insertion site to decrease the risk of infection. CR-BSIs are usually attributed to the migration of bacteria from the skin along the catheter tract. *CR-BSI* is usually defined as more than 15 colony-forming units/mL on semiquantitative culture of the catheter tip. *Catheter-related bacteremia* is defined as bacterial growth and blood cultures that are positive for the same organism as on the catheter tip. Risk factors include infected catheter site or cutaneous breakdown, multiple manipulations, the number of catheter lumens, and the duration of use of the same site (particularly after 3-4 days). Treatment of CR-BSIs should include catheter removal and replacement at another site if necessary.

KEY FACTS

✓ Criteria for weaning from mechanical ventilation—

- patient is hemodynamically stable
- patient's underlying pathophysiologic processes are resolving

  - patient has adequately recovered from respiratory failure

✓ ARDS—use of corticosteroids for treatment in the early stages of the disease is controversial

✓ Indications for central venous access—

  - lack of adequate peripheral veins
  - need for medications or solutions that are hypertonic or phlebitic
  - need for long-term access
  - need for measuring central pressures
  - access for procedures (hemodialysis and cardiac pacing)

✓ Key components of the IHI Central Line Bundle for preventing CR-BSIs—

  - hand hygiene
  - maximal barrier precautions upon insertion
  - chlorhexidine skin antisepsis
  - optimal catheter site selection (with avoidance of femoral vein in adults)
  - daily review of line necessity (with prompt removal of unnecessary lines)

Sepsis

The Society of Critical Care Medicine and the European Society of Intensive Care Medicine have issued a consensus statement on sepsis. In the new definition, *sepsis* is a dysregulated response by the host to an infection that causes life-threatening organ dysfunction. Organ dysfunction is characterized with the Sequential Organ Failure Assessment (SOFA), which incorporates the Pao$_2$:Fio$_2$ ratio, platelet count, Glasgow Coma Scale (GCS) score, bilirubin level, severity of hypotension, and serum creatinine level. *Septic shock* is now defined as a subset of sepsis in a host who has persistent hypotension despite adequate fluid resuscitation and who requires vasoactive medications and therefore has a higher risk of death. *Early sepsis* is identified with the quickSOFA (qSOFA) score, in which points are assigned for a change in mental status (GCS score <15), a fast respiratory rate (≥22 breaths per minute), and low systolic blood pressure (≤100 mm Hg).

A complication is that the evidence that supports the current sepsis management recommendations (2016 version of the Surviving Sepsis Guidelines) is based on prior definitions of *sepsis*. In addition, the Centers for Medicare and Medicaid Services continues to accept prior definitions of sepsis. In the old definitions, *systemic inflammatory response syndrome* (SIRS) was defined as fever or hypothermia, tachycardia, tachypnea, and leukocytosis or leukopenia regardless of cause; *sepsis* was defined as SIRS with a known or presumed source of infection; *severe sepsis* was defined as sepsis associated with organ system dysfunction and systemic effects, including hypotension, decreased urine output, or metabolic acidosis; and *septic shock* referred to persistent signs of organ hypoperfusion despite adequate fluid resuscitation. During this time of transition, clinicians should probably be familiar with both sets of definitions.

The Surviving Sepsis Campaign 2016 includes treatment guidelines for sepsis (Box 73.2).

KEY FACTS

✓ Sepsis—a dysregulated response to an infection that causes life-threatening organ dysfunction

✓ Septic shock (a subset of sepsis)—

  - persistent hypotension despite adequate fluid resuscitation
  - need for vasoactive medications
  - higher risk of death

✓ SOFA (for characterizing organ dysfunction in sepsis)—

  - Pao$_2$:Fio$_2$ ratio
  - platelet count
  - GCS score
  - bilirubin and serum creatinine levels
  - severity of hypotension

✓ qSOFA (for identifying early sepsis)—

  - altered mental status (GCS score <15)
  - high respiratory rate (≥22 breaths per minute)
  - low systolic blood pressure (≤100 mm Hg)

Hemorrhagic Shock

As with sepsis, underresuscitation for shock and hypoperfusion is a common shortfall in the management of intensive care unit (ICU) patients who have clinically significant hemorrhage. When significant blood loss is suspected, the focus should immediately shift to the assessment of perfusion status and to a determination of whether the patient has shock, either overt or cryptic. Hemoglobin and hematocrit should not be used exclusively as quantitative markers of blood loss and determinants of shock. As with other forms of shock, factors that should be assessed include capillary refill time, urine output, presence or absence of altered sensorium, and lactate level and presence of metabolic acidosis. These nonspecific but valuable indicators

Box 73.2 • Sepsis Treatment Recommendations: Surviving Sepsis Campaign 2016

1. Obtain blood or other samples for cultures before starting antibiotic therapy (but do not delay antibiotic therapy).
2. Early during treatment, identify the infectious source, control the source, and administer empirical broad-spectrum antibiotics.
3. Early during treatment, provide fluid resuscitation with 30 mL/kg of crystalloids (in first 3 hours). Administer additional fluids as indicated by frequent reassessment of hemodynamics. For large-volume resuscitation, albumin may be needed.
4. Use norepinephrine as a first-choice vasopressor to maintain mean arterial pressure ≥65 mm Hg. Add a vasopressor or epinephrine if additional vasopressor activity is required.
5. If hemodynamic instability continues despite the above resuscitation, add intravenous hydrocortisone.
6. Monitor lactate levels for normalization to guide resuscitation.
7. De-escalate antibiotic therapy when appropriate, and consider measurement of procalcitonin levels for guidance.
8. When acute respiratory distress syndrome is present, manage it as above.
9. Maintain the blood glucose level at ≤180 mg/dL.
10. Early during treatment, initiate enteral feeding, increasing it as tolerated, with use of prokinetic agents as needed. Initiate parenteral nutrition after 7 days if enteral feeding has not been possible.
11. Discuss goals of care with patients or their families within 72 hours.

Data from Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017 Mar;43(3):304-77.

are helpful in any evaluation of how sick the patient is and how aggressive the resuscitation must be.

Blood loss can be classified according to clinical findings (Table 73.5). Identification of the source of hemorrhage is important, but resuscitation has the highest priority. Patients in the ICU are also at risk for acquired bleeding disorders, especially thrombocytopenia. Patients with thrombocytopenia in the ICU should undergo screening for heparin-induced thrombocytopenia and disseminated intravascular coagulation.

For all patients with clinically significant hemorrhage, several considerations should be addressed immediately (Box 73.3). These considerations, by various mechanisms, can directly influence the initial diagnosis and management of patients with hemorrhagic shock (Box 73.4).

Upper Gastrointestinal Tract Bleeding

Patients with upper gastrointestinal tract bleeding typically present with hematemesis or melena. Patients should be evaluated as described above with priority given to resuscitation as indicated. Endoscopy should be performed within 24 hours. Consideration should be given to administering erythromycin before endoscopy to improve visualization. Typically, proton pump inhibitor therapy is administered as an intravenous bolus followed by twice-daily therapy initially. The goal of endoscopy is to identify the source of bleeding and, more importantly, to use interventional techniques to stop blood loss (eg, injections, clips, or cauterization). Any inciting risk factors for the gastrointestinal tract bleeding (eg, nonsteroidal anti-inflammatory agents) should be discontinued, and *Helicobacter pylori* infection should be treated if identified.

For variceal bleeding, patients should receive a continuous infusion of intravenous octreotide and antibiotic prophylaxis to prevent spontaneous bacterial peritonitis. Endoscopic therapy is typically performed within 12 hours. Variceal ligation has been shown to be more effective than sclerotherapy. Patients with refractory bleeding may require balloon tamponade

Table 73.5 • Classification of Blood Loss

	Class			
Feature	**I**	**II**	**III**	**IV**
Blood loss, mL	<750	750-1,500	1,500-2,000	>2,000
Blood pressure	No change	Systolic: no change Diastolic: increased	Decreased	Hypotension (possibly severe)
Pulse, beats per minute	100	100-120	>120 (thready)	>120-140 (very thready)
Respiratory rate	Normal	Increased	Increased	Increased
Sensorium	Alert, thirsty	Anxious	Anxious or drowsy	Drowsy or obtunded
Urine output	Normal	Decreased	Oliguria	Oliguria or anuria

Box 73.3 • Considerations to Address for a Patient With Significant Hemorrhage

- Presence of shock
- Presence of coagulopathy or thrombocytopenia
- Presence of hypothermia
- Use of medications that exacerbate bleeding, inhibit clotting, or affect platelets (and consideration for discontinuation or reversal if applicable)
- Active alcohol ingestion (for gastrointestinal tract bleeding)
- Active comorbidities that worsen the outcome
- Prior history of hemorrhage that required admission to an intensive care unit
- Presence of severe liver disease (especially with upper gastrointestinal tract bleeding where varices could be a life-threatening concern)
- Recent surgery or procedure that can be associated with bleeding
- Prior history of relevant conditions, such as peptic ulcer disease, polyps, and diverticular disease (for gastrointestinal tract bleeding)

(temporizing treatment) or transjugular intrahepatic portosystemic shunt (definitive treatment).

Lower Gastrointestinal Tract Bleeding

Many patients presenting to an ICU with lower gastrointestinal tract hemorrhage have had a previous episode, and the source of bleeding may be difficult to identify because active bleeding can be intermittent and elusive. Under these circumstances, the utility of emergent colonoscopy, especially in a patient who has not undergone preparation, is not clearly defined because widely disparate diagnostic yields have been reported. Other diagnostic adjuncts, such as arteriography or nuclear medicine scans, may be needed to more precisely identify the source of bleeding when endoscopic findings are uninformative. The treatment of acute lower gastrointestinal tract hemorrhage is largely supportive: resuscitation of the patient, administration of blood, correction of the coagulopathy, and early involvement of other providers (eg, in the gastroenterology and surgery departments) with the care plan.

Box 73.4 • Management Priorities for a Patient With Hemorrhagic Shock

1. Administer necessary fluid and blood resuscitation
2. Correct coagulopathy
3. Reverse or discontinue medications with adverse effects if possible (eg, anticoagulants)
4. Notify the gastroenterology department about the patient and the possible need for emergent endoscopy for gastrointestinal tract bleeding if applicable
5. Consider notifying the surgery department or interventional radiology department if applicable

Fulminant Hepatic Failure

Patients with fulminant hepatic failure most typically present to the ICU without a known history of liver disease. Common causes include toxins; prescription, over-the-counter (eg, acetaminophen), or herbal medications; shock; acute viral hepatitis; autoimmune disease; and vascular catastrophe (Budd-Chiari syndrome). Patients with acute liver failure typically present with overt hepatic synthetic failure with progressive coagulopathy and then worsening encephalopathy. Patients are at risk for dying of complications of hepatic failure, including infection or sepsis, multiorgan failure, and complications of cerebral edema (with or without central nervous system hemorrhage). In the ICU, management and treatment include providing supportive care (Box 73.5), seeking possible causes that are reversible, and advancing to orthotopic liver transplant quickly when the issues described above develop.

Abdominal Compartment Syndrome

Abdominal compartment syndrome (ACS) (also called intra-abdominal hypertension) is the presence of elevated abdominal pressure in the abdominal cavity to the detriment of organ function. Patients at risk include those with severe penetrating and blunt abdominal trauma, ruptured abdominal aortic aneurysm, retroperitoneal hemorrhage, pneumoperitoneum, neoplasm, pancreatitis, massive ascites, liver transplant, abdominal wall burn eschar, abdominal surgery, high-volume fluid resuscitation (>3,500 mL in 24 hours), ileus, and pulmonary, renal, or liver dysfunction.

Box 73.5 • Supportive ICU Care for a Patient With Fulminant Hepatic Failure

- Close surveillance for infections
- Airway protection with endotracheal intubation when encephalopathy or increased intracranial pressure is present
- Aggressive management of coagulopathy
- Intracranial pressure monitoring and therapies when obtundation and evidence of intracranial pressure elevation are present
- Maintenance of the perfusion status of other vital organs (eg, kidneys)

Abbreviation: ICU, intensive care unit.

Patients present clinically with decreased urine output, hypotension, increased respiratory distress with elevated peak pressures, and abdominal distention. Diagnosis can be confirmed with measurement of intra-abdominal pressure (IAP). ACS is defined as a sustained IAP greater than 20 mm Hg (with or without abdominal perfusion pressure <60 mm Hg) that is associated with new organ dysfunction. If elevated IAP is suspected, the bladder pressure can be used to estimate the IAP (but flexing or tensing of abdominal musculature can increase the IAP). Treatment of ACS involves surgical decompression of the abdominal cavity.

Toxicology

If substance overdose is suspected or known, the identity of the substance and the quantity and time of ingestion should be determined. With an overdose of a medicine, the type of dosage form (eg, sustained-release preparation) is also helpful to know because timing, quantity, and preparation all determine how long a patient is at risk from the overdose. Physical examination findings, including vital signs and neurologic findings (especially the status of the pupils), give important clues about the type or severity of ingestion. For example, increases in blood pressure, temperature, and heart rate may occur with overdoses of stimulants such as amphetamines, cocaine, anticholinergics, and sympathomimetics; decreases in blood pressure, temperature, and heart rate may occur with depressants such as narcotics, sedatives, and hypnotics or antihypertensives. Similarly, agitation is suggestive of sympathomimetics and anticholinergics, while depressed mental status suggests an overdose of narcotics or sedatives. Mydriasis may be caused by sympathomimetics, meperidine, and anticholinergics, whereas miosis may result from narcotics and cholinergics. Nystagmus is suggestive of phencyclidine (PCP). In addition to urine toxicology screening, useful diagnostic testing typically includes blood gas analysis, blood glucose level, echocardiography, serum osmolality, electrolyte panel, and acetaminophen and salicylate levels. If acetaminophen overdose is suspected or confirmed, transaminase levels and the international normalized ratio are helpful to know. Typically a drug level specific to the ingestion is obtained if available.

In patients with intoxications and overdoses, multiple ingestions are common, and poison control personnel can be helpful in guiding management. Among the gastrointestinal tract decontaminants used with drug overdoses, charcoal (administered within 1-2 hours after ingestion) is used most often. Ipecac, cathartics, gastric lavage, whole-bowel irrigation, and forced diuresis are almost obsolete in clinical practice. Alkalization of urine (pH>7) is used mostly for overdoses of barbiturates and salicylates. Specific intoxicants, toxidromes, and antidotes are summarized in Table 73.6.

Table 73.6 • Common Intoxicants, Toxidromes, and Their Antidotes

Intoxicant	**Abnormality**	**Antidote**
Acetaminophen	Transaminitis, change in mental status	*N*-acetylcysteine
β-Blockers	↓HR, ↓BP	Glucagon and calcium
Ethylene glycol	Intoxication, ↑AG, renal failure, ↑osmolar gap	Fomepizole
Salicylates	Metabolic acidosis, respiratory alkalosis	Alkalinization of urine, HD
Methanol	Blindness, intoxication, ↑AG, ↑osmolar gap	Fomepizole
SSRIs	↑HR, ↑RR, ↑BP, ↑T, hyperreflexia, rigidity	Cyproheptadine
Cholinergics	DUMBELLSS[a]	Atropine and pralidoxime with or without benzodiazepines
TCAs	↑QRS duration, arrhythmias, anticholinergic symptoms	Alkalinization of serum (bicarbonate drip)
Anticholinergics	↑HR, ↑RR, ↑BP, ↑T, dry skin and mouth, flushed, myoclonus	Physostigmine

Abbreviations: AG, anion gap; BP, blood pressure; HD, hemodialysis; HR, heart rate; RR, respiratory rate; SSRI, selective serotonin reuptake inhibitor; T, temperature; TCA tricyclic antidepressant; ↑, increased; ↓, decreased.

[a] *DUMBELLSS* mnemonic: diarrhea, urination, miosis, bradycardia and bronchospasm, emesis, lacrimation, lethargy, salivation, and seizures.

74 Cystic Fibrosis, Bronchiectasis, and Pleural Effusion

VIVEK N. IYER, MD

Cystic Fibrosis

Cystic fibrosis (CF) is the most common autosomal recessive disease among whites, with a frequency of 1 in 2,000 to 1 in 3,000 live births. In the United States, roughly 30,000 children and adults have CF and another 10 million Americans are disease carriers, and the disease is diagnosed in about 1,000 patients every year. Although CF occurs in all racial and ethnic groups, the incidence is highest in whites of northern European descent. Median life expectancy for patients with CF has been increasing (from 31.3 years in 2002 to 41.1 years in 2012).

CF is caused by a mutation in the gene that encodes for the CF transmembrane conductance regulator (CFTR) on chromosome 7. To date, more than 1,800 mutations in the *CFTR* gene have been identified and are divided into 6 classes (I-VI) depending on their effect on production, membrane translocation, functioning, and turnover of the mutant CFTR protein. This in turn causes production of thick, sticky secretions that clog the airways and the pancreatic and biliary ducts, resulting in chronic cough, frequent sinus and lower respiratory tract infections, progressive bronchiectasis, end-stage lung disease, pancreatic insufficiency, diabetes mellitus, biliary disease, and malabsorption. Infertility is also common in both males and females. Secondary colonization and recurrent infections with many organisms are common (eg, *Staphylococcus aureus, Pseudomonas aeruginosa, Haemophilus influenzae*, nontuberculous mycobacteria, and *Aspergillus*). CF is the most common cause of chronic obstructive pulmonary disease (COPD) and pancreatic deficiency in the first 3 decades of life in the United States.

CF is usually diagnosed before the patient is 2 years old, but for 20% of patients, the diagnosis is not made until adolescence or adulthood. A diagnosis of CF in adults requires the following: 1) clinical symptoms consistent with a diagnosis of CF in at least 1 organ system *and* 2) evidence of CFTR dysfunction as noted by the presence of a sweat chloride level of at least 60 mmol/L on 2 separate occasions, an abnormal nasal potential difference, *or* the identification of 2 disease-causing *CFTR* gene mutations. Sweat chloride testing must be performed with extreme care because inaccurate collection is a common source of misdiagnosis. False-positive results can be from smoking, chronic bronchitis, malnutrition, poor technique, and many other causes. False-negative results can occur in edematous states and in persons receiving corticosteroids. The concentrations of sodium and sweat chloride increase with age.

Treatment of pulmonary manifestations revolves around therapies to promote mucus clearance, including aggressive chest physiotherapy, percussion, postural drainage, and nebulized treatment with hypertonic saline and dornase alfa. Nebulized antibiotics, including tobramycin, aztreonam, and colistin, are often used to reduce the bacterial burden. Daily oral azithromycin is recommended for CF patients 6 years or older who have chronic cough or a reduced forced expiratory volume in the first second of expiration. Prompt treatment of upper and lower respiratory tract infections, adequate hydration, immunizations, and intensive nutritional, physical, and psychologic support are all essential to improving life span and quality of life.

CFTR modulators are a new class of agents that, unlike others, target the basic defect in CFTR function rather than the secondary effects of this defect. They improve functioning of the defective CFTR protein and have a mutation-specific efficacy. Ivacaftor, in 2012, became the first CFTR modulator approved by the US Food and Drug Administration and is currently approved for patients with the G551D mutation and 32 other mutations. Lumacaftor-ivacaftor was the second CFTR modulator approved (for patients with homozygous F508del mutations). Several other CFTR modulators are currently in clinical trials.

Bilateral lung transplant is an option for patients with end-stage lung disease with progressive bronchiectasis and COPD. Infection with *Burkholderia cepacia* is associated with poor outcomes and is generally considered a contraindication for lung transplant.

Bronchiectasis

Bronchiectasis refers to ectasia, or dilatation, of bronchi and bronchioles that typically occurs from repeated lower respiratory tract infections. Tuberculosis is a common cause of bronchiectasis in the developing world. In the United States, bronchiectasis in adults is often secondary to childhood infections, chronic aspiration, immunodeficiency, hypogammaglobinemia, rheumatoid arthritis, Sjögren syndrome, CF, primary ciliary dyskinesia (eg, Kartagener syndrome), and allergic bronchopulmonary aspergillosis (ABPA). In a substantial percentage of patients (30%-40%), no specific cause can be found. Bronchiectasis most commonly involves the lower lung fields; upper lobe involvement may indicate CF, tuberculosis, or nontuberculous mycobacterial disease. ABPA may result in central bronchiectasis with perihilar involvement (finger-in-glove sign).

Key Definition

Bronchiectasis: *dilatation of bronchi and bronchioles that typically occurs after repeated lower respiratory tract infections.*

Classic symptoms of bronchiectasis include chronic cough and copious expectoration of mucopurulent sputum. Nonpulmonary symptoms include fetor oris, anorexia, weight loss, arthralgia, and clubbing. High-resolution computed tomography (HRCT) of the chest is the preferred test for definitive diagnosis. HRCT may also show bronchial obstruction due to inspissated purulent secretions, loss of lung volume, and air-fluid levels. Lung function studies typically show an obstructive pattern with air trapping. Complications of bronchiectasis include hemoptysis, progressive respiratory failure, cor pulmonale, and secondary infections due to fungi and nontuberculous mycobacteria.

Treatment of bronchiectasis is centered on maintaining excellent pulmonary hygiene with use of adequate hydration, chest percussion therapy, postural drainage, hypertonic saline nebulization along with inhaled bronchodilators, and inhaled corticosteroids. For patients with frequent exacerbations (at least 2 or 3 annually), strategies include use of daily azithromycin, which reduces exacerbation rates through both antibiotic and anti-inflammatory effects. Exacerbation frequency may be reduced with cyclic antibiotic therapy with daily or intermittent nonmacrolide oral antibiotics (eg, amoxicillin, levofloxacin, or doxycycline) or nebulized antibiotics (eg, tobramycin, aztreonam, or colistin) or both. Predisposing conditions should be treated aggressively (eg, intravenous immunoglobulin infusions for hypogammaglobinemia, removal of foreign bodies or tumor, and control of aspiration). Surgical resection is reserved for patients with localized disease and complications such as severe hemoptysis.

KEY FACTS

✓ Signs and symptoms of CF—
  - chronic cough, frequent sinus and lower respiratory tract infections, progressive bronchiectasis, end-stage lung disease
  - pancreatic insufficiency, diabetes mellitus
  - biliary disease, malabsorption
  - infertility (in males and females)

✓ Sweat chloride testing—perform with extreme care because inaccurate collection is a common source of misdiagnosis

✓ Treatment of CF—
  - clear the mucus
  - treat upper and lower respiratory tract infections
  - provide adequate hydration, immunizations, and intensive nutritional, physical, and psychologic support

✓ Bronchiectasis—
  - usually affects lower lung lobes (with upper lobe involvement, consider CF, tuberculosis, or nontuberculous mycobacterial disease)
  - classic symptoms: chronic cough and copious expectoration of mucopurulent sputum
  - HRCT of the chest for definitive diagnosis

Pleural Effusion

Patients who have pleural effusions commonly present with dyspnea, nonproductive cough, and pleuritic chest pain. Additional information should be obtained, including a history of weight loss, symptoms of heart failure, malignancy, medication use, and travel and an occupational and exposure history.

The principal causes of pleural effusion are listed in Box 74.1. The diagnosis may be suggested by certain characteristics of the effusion. Pleural fluid testing should be selective and based on clinical suspicion. Despite extensive testing, the cause may remain elusive in up to one-third of patients with pleural effusion.

Box 74.1 • Principal Causes of Pleural Effusion

- Transudate
  - More common
    - Congestive heart failure
    - Cirrhosis, hepatic hydrothorax
    - Atelectasis
    - Hypoalbuminemia
    - Constrictive pericarditis
    - Nephrotic syndrome
  - Less common
    - Peritoneal dialysis
    - Hypothyroidism, myxedema
    - Superior vena cava obstruction
    - Meigs syndrome
    - Urinothorax
- Exudate
  - Infections
    - Parapneumonic (bacterial) effusions
    - Bacterial empyema
    - Fungal infection
  - Tuberculosis
  - Neoplasms
    - Primary and metastatic lung tumors
    - Mesothelioma
  - Pulmonary embolism (up to 20% are transudates)
  - Esophageal rupture
  - Pancreatitis
  - Trauma
  - Connective tissue diseases
    - Rheumatoid arthritis
    - Systemic lupus erythematosus
  - Drug-induced effusions
  - Uremic pleuritis
  - Yellow nail syndrome
  - Dressler syndrome
  - Chylothorax

Distinguishing an Exudate From a Transudate

Traditionally, the Light criteria have been used to identify an exudative effusion, but a meta-analysis found that other findings can also be used to identify fluid as an exudate (Box 74.2). The most common cause of a transudate is congestive heart failure, and the most common cause of an exudate is pneumonia (parapneumonic effusion).

Pleural Fluid Parameters

Glucose and pH

The pleural fluid glucose concentration and pH usually change in the same direction. Glucose levels are low (fluid glucose <60 mg/dL or ratio of fluid glucose to plasma glucose <0.5) in rheumatoid effusion, malignant mesothelioma, systemic lupus erythematosus, esophageal rupture, tuberculous pleurisy, and empyema. Pleural fluid pH is less than 7.30 in empyema, esophageal rupture, rheumatoid effusion, tuberculosis, malignancy, and trauma. A parapneumonic effusion with pH less than 7.20 likely is the result of empyema, and drainage with a chest tube may be required. Empyema caused by *Proteus* species has a pH greater than 7.8 (because of the production of ammonia).

Amylase

The amylase level in pleural fluid is increased in esophageal rupture (because of leakage of salivary amylase), malignancy, pancreatitis, and pancreaticopleural fistula. In any unexplained left-sided effusion, pancreatic disease should be excluded and the pleural fluid amylase level should be estimated.

Chylous Effusion

Chylous effusion is suggested by a turbid or milky white appearance of the fluid. The pleural fluid triglyceride concentration is often greater than 110 mg/dL. A concentration less

Box 74.2 • Criteria for Identifying an Exudate

Light criteria—fluid is an exudate if any 1 of the following is present:

1. Ratio of pleural fluid protein to serum protein >0.5
2. Ratio of pleural fluid LDH to serum LDH >0.6
3. Pleural fluid LDH >67% of the upper limit of the reference range for serum LDH

Other criteria—fluid is an exudate if any 1 of the following is present:

1. Pleural fluid protein >2.9 g/dL
2. Pleural fluid cholesterol >45 mg/dL
3. Pleural fluid LDH >0.45 times the upper limit of the reference range for serum LDH

Abbreviation: LDH, lactate dehydrogenase.

Box 74.3 • Mnemonic for Causes of Chylous Effusion: 5 *T*'s

Thoracic duct
Trauma
Tumor (lymphoma)
Tuberculosis
Tuberous sclerosis (lymphangiomyomatosis)

than 50 mg/dL excludes chylothorax. A helpful mnemonic for causes of chylous effusion is 5 *T*'s (Box 74.3). Lymphoma is the most common nontraumatic cause of chylothorax.

Cell Counts

A **hemorrhagic effusion** (pleural fluid hematocrit >50% of serum hematocrit) occurs in trauma, tumor, asbestos effusion, pancreatitis, pulmonary embolism with infarctions, and other conditions. A bloody effusion in lung cancer usually denotes pleural metastasis, even if the cytologic results are negative. Pleural fluid eosinophilia (>10%) is nonspecific and occurs with air or blood in the pleural space, fungal infections, drug-induced effusions, and malignancy. Pleural fluid lymphocytosis is most commonly associated with tuberculosis but can also occur with chronic effusions, lymphoma, sarcoidosis, chylothorax, and chronic rheumatoid pleurisy.

Key Definition

Hemorrhagic effusion: *bloody pleural fluid with a hematocrit >50% of the serum hematocrit.*

Cytology

Cytologic examination is an important test if patients have a known or suspected malignancy. Diagnostic yields are improved with more than 1 thoracentesis but remain in the 50% to 60% range. A positive fluid cytology finding in primary lung carcinoma implies late-stage, unresectable disease.

Cultures

Pleural fluid should be inoculated directly into aerobic, anaerobic, and fungal blood culture bottles to increase diagnostic yield. For patients with suspected tuberculosis, culture of pleural biopsy specimens is also useful. The diagnosis of pleural tuberculosis often requires the combination of several techniques, including determining the level of pleural fluid adenosine deaminase.

Pleural Biopsy

Pleural biopsies can be obtained percutaneously or with medical thoracoscopy, which is an outpatient procedure that allows for visualization of the entire pleural lining. Medical thoracoscopy is useful for recurrent effusions of undetermined cause and in certain conditions such as malignancy and tuberculosis.

KEY FACTS

- ✓ Pleural effusion—dyspnea, nonproductive cough, and pleuritic chest pain
- ✓ Most common cause of transudate—congestive heart failure
- ✓ Most common cause of exudate—pneumonia (parapneumonic effusion)
- ✓ Parapneumonic effusion with pH <7.20—likely from empyema that requires drainage with a chest tube
- ✓ Mnemonic for causes of chylous effusion—5 *T*'s: thoracic duct, trauma, tumor, tuberculosis, tuberous sclerosis
- ✓ Positive findings on fluid cytology in primary lung carcinoma—late-stage, unresectable disease
- ✓ Diagnosis of pleural tuberculosis—may need several techniques, including determining the level of pleural fluid adenosine deaminase

Special Considerations

Parapneumonic Effusions

Pleural effusions occurring on the same side as a bacterial pneumonia are termed parapneumonic effusions. They can be classified as *uncomplicated* (exudative effusion with a normal pH, a normal glucose level, and negative cultures); *complicated* (exudative effusion with a low pH and a low glucose level, and they are often loculated); and *empyema* (with any of the following: frank pus, positive cultures, and Gram stain). Complicated parapneumonic effusions and empyema should be drained promptly to avoid complications. The use of intrapleural tissue plasminogen activator and deoxyribonuclease may accelerate resolution of effusions that are loculated or partially drained with ongoing signs of infection.

Malignant Effusions

The finding of malignant cells in the pleural fluid points to the diagnosis of a malignant pleural effusion, which typically occur with metastatic disease (eg, seeding of the pleural space from the primary cancer), lymphoma, and other hematologic malignancies and mesothelioma. These effusions typically recur and often require repeated thoracentesis, placement of an indwelling pleural catheter, or talc pleurodesis. Treatment is tailored according to expected survival from the underlying malignancy and the patient's functional status and effusion-related symptoms.

Hepatic Hydrothorax

Hepatic hydrothorax is diagnosed when a large pleural effusion occurs in a patient with cirrhosis without other obvious cardiac, pulmonary, or pleural causes. It occurs predominantly on the right side because of movement of ascitic fluid into the pleural space through small diaphragmatic defects. Treatment is similar to the management of ascites, including managing underlying liver disease, fluid and sodium restriction, diuretics, thoracentesis, and placement of a transjugular intrahepatic portosystemic shunt in refractory cases.

Complications of Thoracentesis

Complications of thoracentesis have been greatly reduced by the use of sterile technique and ultrasonographic guidance. Complications include pneumothorax, hemothorax, pulmonary edema, intrapulmonary hemorrhage, hemoptysis, vasovagal reaction, air embolism, subcutaneous emphysema empyema, seeding of a needle tract with malignant cells, and puncture of the liver or spleen.

75 Interstitial Lung Diseases

JEREMY M. CLAIN, MD; TIMOTHY R. AKSAMIT, MD

Diagnosis

A**n estimated 1** in 3,000 to 1 in 4,000 persons in the general population have a diagnosis of **interstitial lung disease** (ILD), and ILDs account for about 15% of all consultations for general pulmonologists. These diseases encompass a group of heterogeneous lung conditions characterized by diffuse involvement of the lung parenchyma and pulmonary interstitium (Box 75.1). Infections, pulmonary edema, lung malignancies, and emphysema are excluded by convention, but they should be carefully considered as part of the differential diagnosis (Box 75.2).

Key Definition

Interstitial lung disease: *a heterogeneous group of lung conditions that are characterized by diffuse involvement of the lung parenchyma and pulmonary interstitium and that exclude infections, pulmonary edema, lung malignancies, and emphysema.*

Some ILDs are characterized by suggestive or even pathognomonic findings, but the majority are best diagnosed through a dynamic interaction between clinicians, radiologists, and pathologists. Prompt recognition of ILD and initiation of appropriate therapy can greatly improve otherwise potentially life-threatening respiratory conditions. The 4 major categories of ILD are 1) ILDs of known cause (eg, drug-induced lung disease and connective tissue disease–related ILD [CTD-ILD]), 2) idiopathic interstitial pneumonias (Box 75.3), 3) granulomatous ILDs (eg, sarcoidosis and hypersensitivity pneumonitis [HP]), and 4) other ILDs (usually readily recognizable from characteristic findings).

The strategy for diagnosing ILD should follow a stepwise approach, including 1) a comprehensive history and thorough physical examination, 2) pulmonary function tests (PFTs), 3) radiologic studies (usually including high-resolution computed tomography [HRCT]), and, if needed, 4) lung biopsy (bronchoscopic or surgical or both) (Figure 75.1). However, all tests are not necessary for the majority of patients, and the diagnosis may be achieved without histologic confirmation.

History

A detailed history is the most important step in the diagnosis of ILD (Table 75.1). Environmental exposures (eg, pets, organic material, or mineral dust) or occupational exposures should be comprehensively investigated.

Physical Examination

Rales ("dry crackles" or "Velcro crackles") suggest fibrosis but are nonspecific. Clubbing of the digits can be associated with idiopathic pulmonary fibrosis (IPF) and asbestosis but is rarely associated with other forms of ILD. Clubbing should raise concerns for alternative diagnoses (eg, lung or pleural malignancies, chronic suppurative lung diseases, or a right-to-left shunt). Careful attention should be paid to extrapulmonary manifestations of systemic diseases, such as musculoskeletal pain, sicca syndrome, and Raynaud phenomenon.

Pulmonary Function Studies

Typically, PFTs show a restrictive pattern, as evidenced by decreased lung volumes and preservation of flows. The diffusing capacity of lung for carbon monoxide (DLCO) is also

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The editors and authors acknowledge the contributions of Fabien Maldanado, MD, to the previous edition of this chapter.

Box 75.1 • Causes of Interstitial Lung Disease

- Collagen vascular
  - Inflammatory myopathy
  - Rheumatoid arthritis
  - Scleroderma
  - Sjögren syndrome
- Therapy-induced
  - Chemotherapy
  - Drug therapy
  - Radiotherapy
- Genetic
  - Hermansky-Pudlak syndrome
  - Metabolic storage disease
  - Neurofibromatosis
  - Tuberous sclerosis
- Idiopathic
- Occupational or inhalational
  - Asbestosis
  - Coal workers' pneumoconiosis
  - Hypersensitivity pneumonitis
  - Silicosis
  - Toxic gas
- Sarcoidosis
- Vasculitides
  - Eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome)
  - Giant cell arteritis
  - Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis)

Box 75.2 • Causes of Diffuse Pulmonary Abnormalities Excluded From the Definition of Interstitial Lung Disease

- Cardiogenic pulmonary edema
- Emphysema
- Chronic infection
  - Mycobacterial
  - Mycotic
- Malignancy
  - Adenocarcinoma in situ
  - Lymphangitic metastases
  - Lymphoma

Box 75.3 • Idiopathic Interstitial Lung Disease

- Idiopathic pulmonary fibrosis (IPF) (associated with a histopathologic or radiologic pattern of usual interstitial pneumonia [UIP])
- Nonspecific interstitial pneumonia (NSIP)
- Cryptogenic organizing pneumonia (COP) (formerly called idiopathic bronchiolitis obliterans with organizing pneumonia [BOOP])
- Eosinophilic lung diseases
- Lymphocytic interstitial pneumonia (LIP)
- Alveolar microlithiasis
- Lymphangioleiomyomatosis (LAM)
- Langerhans cell histiocytosis (pathologically, eosinophilic granulomatosis)
- Pulmonary alveolar proteinosis
- Acute respiratory distress syndrome (formerly called acute lung injury)

reduced. When DLCO is reduced out of proportion to the rest of the PFTs, concurrent pulmonary hypertension or emphysema may be present.

Imaging Studies

Although chest radiography has been largely supplanted by HRCT, several characteristic imaging findings are useful (Box 75.4). HRCT has revolutionized the diagnosis of ILD and often obviates the need for histopathologic examination. Several characteristic features should narrow the differential diagnosis. Alveolar opacities (consolidation or ground-glass infiltrates) suggest reversible disease, while reticular "fibrotic" infiltrates are less likely to resolve. Honeycombing, traction bronchiectases, and basal predominance are typical for usual interstitial pneumonia (UIP), a pattern necessary for the diagnosis of IPF (see section on IPF below). Thin-walled cysts suggest pulmonary Langerhans cell histiocytosis (PLCH) (upper lobe predominance) or lymphangioleiomyomatosis (LAM) (diffuse lung involvement). A crazy-paving pattern (ground-glass infiltrates with septal thickening) is seen in pulmonary alveolar proteinosis (PAP).

Laboratory Studies

Laboratory studies are rarely helpful in the diagnosis of ILD. Useful tests include a complete blood cell count with a differential blood count, liver and renal function tests, and connective tissue disease serologies. Hepatitis and human immunodeficiency virus serologies may also be indicated. Depending on the clinical picture, other laboratory studies can be considered (Box 75.5).

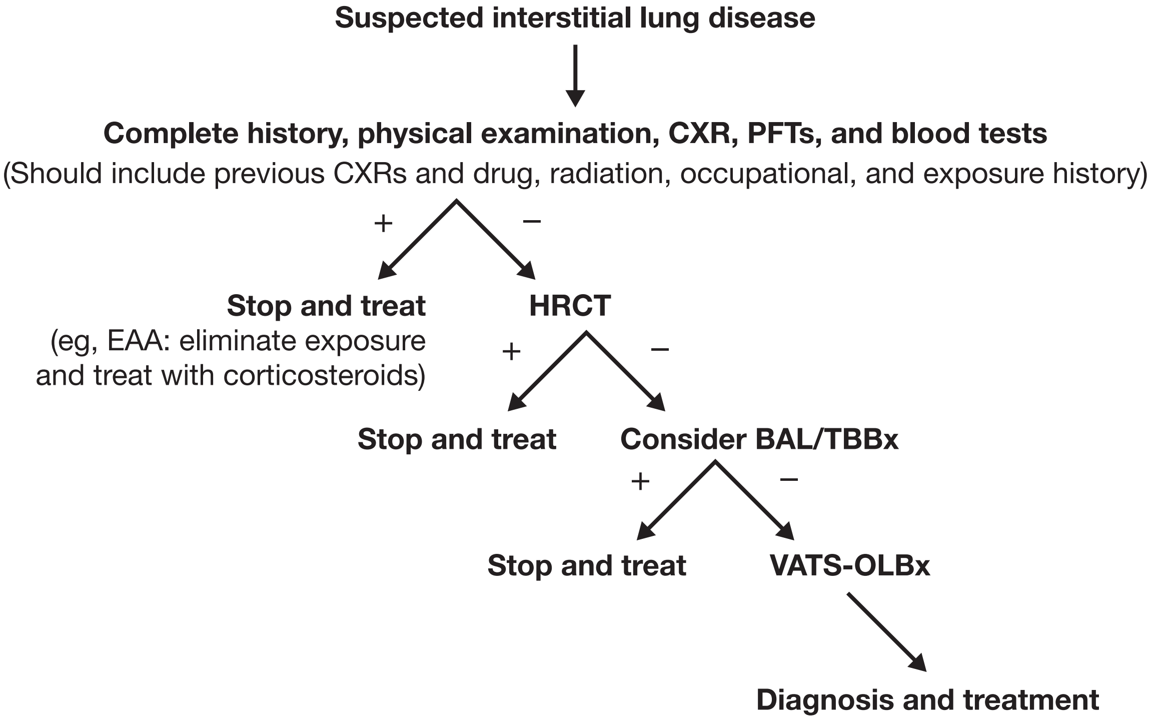
Suspected interstitial lung disease
Complete history, physical examination, CXR, PFTs, and blood tests
(Should include previous CXRs and drug, radiation, occupational, and exposure history)
+
−
Stop and treat
(eg, EAA: eliminate exposure and treat with corticosteroids)
HRCT
+
−
Stop and treat
Consider BAL/TBBx
+
−
Stop and treat
VATS-OLBx
Diagnosis and treatment

Figure 75.1. *Strategy for Diagnosing Interstitial Lung Disease. BAL indicates bronchoalveolar lavage; CXR, chest radiography; EAA, extrinsic allergic alveolitis; HRCT, high-resolution computed tomography; OLBx, open lung biopsy; PFT, pulmonary function test; TBBx, transbronchial biopsy; VATS, video-assisted thoracoscopy; +, positive findings; −, negative findings.*

Table 75.1 • Interstitial Lung Diseases Distinguished by History

Exposure or Feature	Disease
Amiodarone, methotrexate, nitrofurantoin, chemotherapy, radiotherapy	Drug-induced or iatrogenic lung disease
Insulation work, shipbuilding, mining, sandblasting	Pneumoconioses
Birds, indoor hot tubs, moldy humidifiers	Hypersensitivity pneumonitis
Acute onset of disease	Acute eosinophilic pneumonia or organizing pneumonia Virtually rules out IPF and asbestosis (which evolve over months to years)
Current smoker	Desquamative interstitial pneumonia, respiratory bronchiolitis–associated interstitial lung disease, IPF, pulmonary Langerhans cell histiocytosis
Former smoker or never smoker	Sarcoidosis, hypersensitivity pneumonitis

Abbreviation: IPF, idiopathic pulmonary fibrosis.

Histopathologic Diagnosis

Bronchoscopy is often performed, primarily to exclude infection before immunosuppressive therapy is started. Traditional bronchoscopic biopsies typically do not provide sufficient tissue to establish the diagnosis of ILD, but some features on bronchoalveolar lavage may have diagnostic value (Box 75.6). Surgical lung biopsy has improved diagnostic yield but is usually reserved for younger patients for whom a confident diagnosis is necessary to guide treatment decisions. Bronchoscopic cryobiopsy has been introduced as an alternative to surgical lung biopsy, but the role of cryobiopsy in the diagnosis of ILD is not yet well established. For both surgical and bronchoscopic cryobiopsy, the risks and benefits need to be weighed and discussed with the patient, because acute exacerbations of ILD may be provoked by biopsy, at times with dramatic consequences.

KEY FACTS

✓ Diagnosis of ILDs—

- some ILDs have suggestive or pathognomonic findings
- most ILD diagnoses require dynamic interaction between clinicians, radiologists, and pathologists

  - collecting a detailed history is the most important step
  - thoroughly investigate environmental and occupational exposures
  - if clubbing is present, consider another diagnosis (eg, lung or pleural malignancy, chronic suppurative lung disease, or a right-to-left shunt)

✓ PFT findings in ILD—

  - restrictive pattern (decreased lung volumes and preservation of flows)
  - decreased Dlco (if Dlco is decreased out of proportion to the rest of the PFTs, the patient may have concurrent pulmonary hypertension or emphysema)

✓ Imaging findings in ILD—

  - mnemonic *CHAPS* for remembering predominant upper lung opacities
  - IPF and asbestosis predominate in lower lung areas
  - alveolar infiltrates in a "bat wing" distribution are typical of PAP or cardiogenic pulmonary edema
  - pneumothorax may be a clinical manifestation of PLCH and LAM

Box 75.4 • Characteristic Imaging Findings in Patients With Interstitial Lung Disease

Distribution of infiltrates may provide guidance

The mnemonic *CHAPS* is useful for remembering upper lobe–predominant opacities:

C—cystic fibrosis, chronic eosinophilic pneumonia

H—HP, histiocytosis (PLCH)

A—allergic bronchopulmonary aspergillosis, ankylosing spondylitis

P—pneumoconioses

S—sarcoidosis and silicosis

IPF and asbestosis predominate in lower lung areas

Bilateral hilar lymphadenopathy suggests sarcoidosis or silicosis

Alveolar infiltrates in a "bat wing" distribution are typical of PAP or cardiogenic pulmonary edema

Peripheral opacities ("photographic negative of pulmonary edema") have been described in chronic eosinophilic pneumonia

Pneumothorax may be the clinical manifestation of PLCH and LAM

Abbreviations: HP, hypersensitivity pneumonitis; IPF, idiopathic pulmonary fibrosis; LAM, lymphangioleiomyomatosis; PAP, pulmonary alveolar proteinosis; PLCH, pulmonary Langerhans cell histiocytosis.

Box 75.5 • Laboratory Studies That May Be Useful in the Diagnosis of ILD

Complete blood cell count with differential blood count

Liver function tests

Renal function tests

Serologies for hepatitis and HIV

Serologies for connective tissue disease in OP and NSIP

Serum protein electrophoresis if amyloidosis is in the differential diagnosis

Hypersensitivity pneumonitis antibody testing (rarely helpful in practice)

Angiotensin-converting enzyme level (classically used to follow patients with sarcoidosis, but it is neither sensitive nor specific)

ANCA studies if ANCA-associated vasculitis is in the differential diagnosis

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; ILD, interstitial lung disease; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia.

ILDs of Known Cause

Connective Tissue Disease–Related Interstitial Lung Diseases

Virtually all connective tissue diseases may affect the lungs. CTD-ILDs are more common in females, with the exception of rheumatoid arthritis (RA), which is more common in men. The typical histopathologic patterns seen with CTD-ILD are nonspecific interstitial pneumonia (NSIP) and organizing pneumonia (OP). The differential diagnosis for a patient being evaluated for potential CTD-ILD should account for the fact that many disease-modifying agents used to treat an underlying connective tissue disease can cause pulmonary inflammation or increase the patient's risk of atypical infection.

Rheumatoid Arthritis

RA-related ILD (RA-ILD) differs from other CTD-ILDs: RA-ILD is more common in males and typically has a UIP pattern, which is less responsive to treatment and carries a poor prognosis. RA is commonly associated with pleural effusions, pulmonary nodules, and fibrosis (RA-ILD), but it may affect any part of the respiratory system.

Systemic Lupus Erythematosus

Systemic lupus erythematosus typically causes NSIP or OP (or both). A life-threatening, rare, pulmonary complication is acute lupus pneumonitis, characterized by diffuse alveolar damage, which is identified from lung biopsy and is poorly responsive to treatment. Diaphragmatic weakness (myopathy) may result in subsegmental atelectasis (also called platelike atelectasis) or, when severe, the classic shrinking lung syndrome,

Box 75.6 • Diagnostic Utility of Bronchoalveolar Lavage Findings in the Diagnosis of ILD

A predominance of lymphocytes is consistent with sarcoidosis (with a classically inverted CD4:CD8 ratio, typically >4) or hypersensitivity pneumonitis (with a normal or decreased CD4:CD8 ratio)

Eosinophilic predominance is seen with acute and chronic eosinophilic pneumonia

Hemosiderin-laden macrophages are seen in diffuse alveolar hemorrhage

Lipid-laden macrophages are seen in aspiration pneumonia and, less commonly, in lipoid pneumonia

If >5% of cells have antigen CD1a (a marker of Langerhans histiocytes), PLCH is a possibility

Abbreviations: ILD, interstitial lung disease; PLCH, pulmonary Langerhans cell histiocytosis.

which is characterized by low lung volumes in the absence of interstitial lung infiltrates.

Inflammatory Myopathies

Inflammatory myopathies (dermatomyositis and polymyositis) may cause NSIP and OP, respiratory muscle weakness, and recurrent aspiration. Clinical manifestations include lung fibrosis, arthritis, Raynaud phenomenon, and myositis. The finding of an eczematous condition called mechanic's hands is a clue to lung involvement (Figure 75.2).

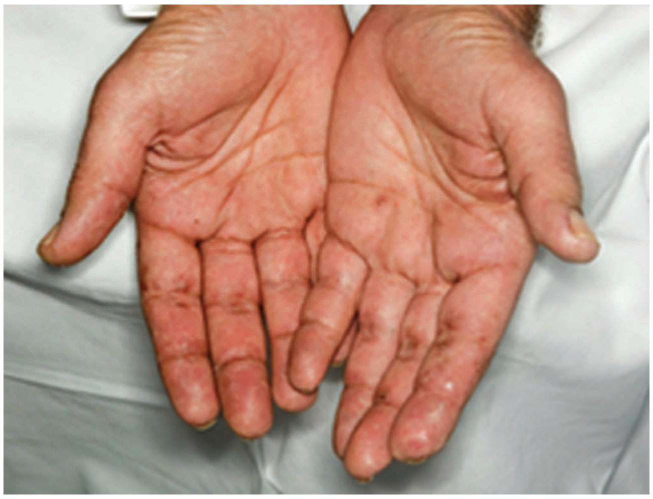

Figure 75.2. *Dermatomyositis. Mechanic's hands are characterized by roughening and fissures of the skin on the lateral and palmar areas of the fingers.*

(From Khambatta S, Wittich CM. Amyopathic dermatomyositis. Mayo Clin Proc. 2010 Nov;85[11]:e82; used with permission of Mayo Foundation for Medical Education and Research.)

Scleroderma

Scleroderma (systemic sclerosis) is associated with fibrosis and pulmonary hypertension (in up to 25% of the patients), particularly in limited scleroderma or **CREST syndrome** (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia). Scleroderma may also cause recurrent aspiration from esophageal dysmotility.

Key Definition

CREST syndrome: *a limited form of scleroderma that consists of calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia.*

Sjögren Syndrome

As with other connective tissue diseases, Sjögren syndrome is associated with NSIP and OP. In addition, lymphocytic interstitial pneumonia (thought to be a low-grade lymphoproliferative disorder) is a classic manifestation of Sjögren lung disease.

Drug- and Therapy-Induced Lung Diseases

Various pharmacologic agents may cause drug-induced lung disease. Discontinuing use of the drug is mandatory and usually results in prompt clinical improvement. The use of corticosteroids is often recommended, particularly for severe disease manifesting with hypoxia, but the evidence for this practice is anecdotal at best. The common offenders discussed below should be presumed to be responsible for lung disease until proved otherwise.

Bleomycin Lung Toxicity

Bleomycin lung toxicity is the prototype of drug-induced lung disease. Bleomycin is an antibiotic chemotherapeutic agent used in various malignancies, primarily Hodgkin disease. The toxicity is cumulative, resulting in progressive fibrosis that may be indistinguishable from IPF.

Methotrexate

Methotrexate may cause a sarcoidosis-like reaction, with bilateral hilar lymphadenopathy and diffuse lung infiltrates. Eosinophilia is present in 50% of the patients. Bronchoscopic lung biopsies may show ill-defined granulomas, and the cell count and differential count on bronchoalveolar lavage are similar to those in sarcoidosis with lymphocytic predominance.

Nitrofurantoin

Nitrofurantoin is an antibiotic used to treat and prevent urinary tract infections. It may cause life-threatening, acute forms of lung toxicity (eosinophilic pneumonia) in 1 in 500 to 1 in 5,000 patients. A chronic form, similar in presentation to IPF, occurs in 1 in 50,000 patients (generally patients receiving long-term nitrofurantoin therapy for suppression of recurrent urinary tract infections). Discontinuing use of the drug is mandatory.

Amiodarone

Amiodarone can cause lung toxicity, which is cumulative in most patients after exposure to amiodarone at a dosage of more than 400 mg daily for 3 to 6 months. One particular radiologic characteristic of amiodarone lung toxicity is the presence of high-attenuation infiltrates on noncontrast HRCT, a result of the high iodine content of amiodarone. Treatment consists of discontinuing use of the drug, but because of its long half-life (2-3 months), clinical improvement may be delayed.

Pneumoconioses

Asbestos-Related Lung Diseases

Asbestos-related lung diseases should be suspected in patients with occupations that expose them to asbestos (eg, insulation work, shipbuilding, and mining). Most pulmonary manifestations occur after a dormant period of 20 to 40 years, except for benign asbestos-related pleural effusion, which may occur within 10 years after exposure. Calcified pleural (or pericardial) plaques are a marker for asbestos exposure, but they do not generally cause symptoms. Other lung manifestations are listed in Box 75.7.

Silicosis

Silicosis occurs in patients exposed to silica (eg, through mining, quarrying, and sandblasting). The disease is distinct from asbestosis, and findings include bilateral hilar lymphadenopathy (occasionally eggshell calcifications) with clustered micronodular infiltrates that typically favor the apices of the lungs. Silicosis has 3 characteristic associations: 1) Silicosis is a risk factor for tuberculosis, which should be excluded in patients whose respiratory condition worsens. 2) An association with connective tissue diseases has been described (Caplan syndrome). 3) Silicosis may be an independent risk factor for lung cancer, although to a much lesser extent than asbestos exposure.

Box 75.7 • Lung Manifestations of Asbestos Exposure

- Calcified pleural (or pericardial) plaques
- Asbestosis
  - An ILD with similarities to IPF, but asbestosis carries a better prognosis
  - Treatment is supportive; corticosteroids are not indicated
- Rounded atelectasis
  - A focal subpleural opacity with the comet tail sign; often confused with lung cancer
- Malignancy
  - Mesothelioma—a primary pleural malignancy that carries a poor prognosis; therapeutic options are few
  - Bronchogenic carcinoma—although smoking is not a risk factor for mesothelioma, it acts synergistically with asbestos exposure and exponentially increases the risk of bronchogenic carcinoma

Abbreviations: ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.

KEY FACTS

- ✓ CTD-ILD—typical histopathologic patterns are NSIP and OP
- ✓ RA-ILD—typical histopathologic pattern is UIP (less responsive to treatment than other CTD-ILDs and carries a poor prognosis)
- ✓ Mechanic's hands—a clue to lung involvement in inflammatory myopathies
- ✓ Drug-induced lung disease—after use of the drug is stopped, clinical improvement is usually prompt
- ✓ Asbestos exposure—
  - calcified pleural (or pericardial) plaques are a marker, but they do not usually cause symptoms
  - smoking is not a risk factor for mesothelioma
  - smoking acts synergistically with asbestos exposure and exponentially increases the risk of bronchogenic carcinoma
- ✓ Silicosis—
  - a risk factor for tuberculosis (a consideration if a patient's respiratory condition worsens)
  - possibly an independent risk factor for lung cancer (but to a much lesser extent than asbestos exposure)

Idiopathic Interstitial Pneumonias

Idiopathic Pulmonary Fibrosis

IPF is the most common idiopathic interstitial pneumonia, and it usually affects men and women older than 50 years. A complete understanding of the pathophysiology remains elusive, but the condition is thought to result from recurrent pulmonary injury with an exuberant fibrotic response. The fibrosis of IPF tends to progress over time, but rates of disease advancement are variable. Two antifibrotic agents, nintedanib and pirfenidone, have been approved for slowing the rate of progression of IPF, but no treatments are available to reverse existing fibrosis. Corticosteroids should not be used. Lung transplant is an option for select patients.

The histopathologic findings in IPF are described as UIP, and the typical, corresponding radiographic findings are described as a UIP pattern: a basilar and peripheral distribution, honeycombing, traction bronchiectasis, and minimal ground-glass opacities. However, a UIP pattern is not pathognomonic for IPF. Rather, the diagnosis of IPF depends on both the identification of a UIP pattern (either histopathological or radiographic) and the exclusion of other possible causes of UIP, such as asbestosis, drug-induced lung disease, HP, and CTD-ILD. Since a radiographic UIP pattern satisfies the diagnostic criteria, a lung biopsy is not necessary to establish a diagnosis of IPF. In fact, biopsy is frequently avoided because it may precipitate an acute exacerbation, a life-threatening complication of IPF. The prognosis is poor: Median survival before the advent of antifibrotic medications was approximately 3 to 5 years, but the prognosis for patients receiving antifibrotic therapy has not yet been completely defined.

Nonspecific Interstitial Pneumonia

NSIP is the main differential diagnosis for IPF. Patients with NSIP usually present at a younger age (<50 years) and females predominate over males (2:1). The frequent presence of autoantibodies suggests that NSIP may be, at least in some patients, an autoimmune process. Radiologically, NSIP shows diffuse involvement of the lungs, ground-glass opacities, and limited honeycombing and traction bronchiectases. NSIP is also a histopathologic diagnosis that may occur in other diseases (eg, CTD-ILD, HP, and infections). Treatment with corticosteroids or corticosteroid-sparing immunosuppressive agents (or both) is often effective, and the 5-year survival (about 80%) is much better than with IPF.

Smoking-Related Idiopathic Interstitial Pneumonias

Respiratory bronchiolitis–associated ILD (RB-ILD) and desquamative interstitial pneumonia (DIP) compose the smoking-related idiopathic interstitial pneumonias, and both entities derive from intrapulmonary macrophage accumulation. The finding of pigmented macrophages within bronchiole lumens is nearly universal in active smokers and is referred to as *respiratory bronchiolitis*. RB-ILD occurs in rare instances when this inflammatory response to smoking is so extensive that it causes respiratory symptoms and bronchiolocentric interstitial abnormalities. Intraluminal pigmented macrophages are also a defining histopathologic feature in DIP, but the interstitial abnormalities in DIP are more diffuse than in RB-ILD. The mainstay of therapy for both entities is smoking cessation, and the prognosis is generally favorable, particularly compared with the prognosis for patients with IPF.

Cryptogenic Organizing Pneumonia

Cryptogenic organizing pneumonia (COP) was formerly known as idiopathic bronchiolitis obliterans with organizing pneumonia (BOOP). Typically, COP manifests as a recurrent flulike illness that is resistant to antibiotics and has migratory infiltrates that progress over several months. The radiologic features include consolidation and ground-glass infiltrates (usually peripheral), and the pattern on PFTs is that of restriction rather than obstruction. COP is exquisitely responsive to treatment with corticosteroids, which should be administered for 3 to 6 months. Rebound after discontinuation is common, but COP generally responds to additional treatment with corticosteroids. Prolonged macrolide therapy is sometimes useful while systemic corticosteroid doses are being tapered.

Acute Interstitial Pneumonia

Acute interstitial pneumonia (AIP), or Hamman-Rich syndrome, is characterized histologically by diffuse alveolar damage (with the presence of hyaline membranes), the histologic hallmark of acute respiratory distress syndrome (ARDS). In fact, the term *AIP* is equivalent to *idiopathic ARDS*. As with ARDS, the mortality is high (about 50%), but survivors have the potential for nearly complete respiratory recovery.

KEY FACTS

✓ IPF—
- poor prognosis
- median survival, 3-5 years
- exclude other conditions associated with UIP (which may be more responsive to therapy)

✓ NSIP—
- a histopathologic diagnosis that may occur in other diseases (eg, CTD-ILD, HP, and infections)
- corticosteroid therapy is often effective
- 5-year survival, about 80% (much better than with IPF)

✓ COP—corticosteroid therapy for 3-6 months

Granulomatous ILDs

The most common causes of granulomatous lung disease are infections, which are usually due to mycobacterial or fungal organisms. Multiple forms of inflammatory granulomatous lung disease also occur, which must be distinguished from one another and from infectious causes.

Sarcoidosis

Sarcoidosis is a granulomatous disease of unknown cause that typically affects patients younger than 50 years (African American females predominate). Patients may present with acute or gradual-onset lung disease, with possible progression toward end-stage diffuse fibrotic lung disease.

Sarcoidosis is one of the few lung diseases that predominantly affect nonsmokers and former nonsmokers (along with HP). Although the lungs (in >90% of patients) and lymph nodes are the most commonly involved organs, the disease can affect virtually any organ, including the heart, liver, spleen, eye, bone, skin, bone marrow, parotid glands, pituitary, and reproductive organs, and the nervous system. Hypercalcemia, anemia, and increased liver enzyme levels may be noted. Familial clusters of sarcoidosis have been reported. The course of the disease is highly variable, from asymptomatic to life-threatening.

Imaging

The radiographic stage of sarcoidosis correlates with the severity of pulmonary disease and prognosis (Box 75.8). Chest radiography may also show characteristic bilateral hilar or mediastinal lymphadenopathy with occasional eggshell calcifications. Computed tomography of the chest may show clustered micronodules, often with a perilymphatic distribution.

Diagnosis

In most patients with sarcoidosis, granulomatous inflammation needs to be identified and other causes of granulomatous inflammation excluded (primarily fungal, mycobacterial, and other infections). Thus, sarcoidosis must be considered a diagnosis of exclusion after other causes of granulomatous disease have been ruled out. The serum levels of angiotensin-converting enzyme (ACE) are not sufficiently sensitive or specific to be of diagnostic value, and the utility of monitoring ACE levels as a marker of disease activity is uncertain.

Treatment

Corticosteroids are first-line therapy. Other immunosuppressive regimens used as second-line therapy for pulmonary sarcoidosis have included methotrexate, azathioprine, leflunomide, and infliximab. Treatment is reserved for severe organ disease (including progressive lung disease). In up to 90% of patients with stage I pulmonary sarcoidosis, the disease is expected to remain stable or to resolve spontaneously with no treatment. Stage III pulmonary sarcoidosis is expected to spontaneously remit in only 10% of patients. Pulmonary sarcoidosis is expected to progress within 2 to 5 years after diagnosis, although increased disease activity can occur at any time.

Box 75.8 • Radiographic Stages of Sarcoidosis

Stage 0—normal findings on chest radiography
Stage I—hilar adenopathy
Stage II—hilar adenopathy with pulmonary infiltrates
Stage III—pulmonary infiltrates without adenopathy
Stage IV—fibrotic lung disease

Hypersensitivity Pneumonitis

HP is an uncommon form of ILD. It is considered an allergic reaction to various organic antigens, including molds, grain dusts (farmer's lung), pets and birds (bird fancier's lung), and mycobacterial antigens (hot tub lung). Serum tests for specific antigens have poor sensitivity and specificity. The symptoms and clinical course are related temporally to antigen exposure. With acute disease, patients may have dyspnea, cough, fever, chest pain, headache, malaise, fatigue, and flulike illness. Chronic diffuse fibrotic lung disease may be indistinguishable from IPF.

The histopathologic features of HP show a range of bronchiolar-oriented, ill-defined, noncaseating granulomas. A restrictive pattern is common on PFTs, although an airway component may also be present and result in an obstructive component. Bronchodilators may be needed to treat airflow obstruction. Chest radiography generally shows reticulonodular changes, and HRCT often shows nonspecific nodules and ground-glass opacities predominantly in the upper lobes. Acute symptoms generally improve after the patient is no longer exposed to the antigen. Patients with severe HP also require treatment with corticosteroids, and patients with chronic HP may benefit from long-term maintenance therapy with corticosteroid-sparing agents as an adjunct to antigen avoidance.

Other Granulomatous Diseases

Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) and eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome) are forms of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis that can occur in whole or in part with granulomatous lung disease. ANCA serologies and a history of compatible extrapulmonary symptoms may be helpful in making these diagnoses.

Foreign materials can also lead to granulomatous lung disease. Intravenous injection of insoluble material, such as intravenous talcosis (as occurs in intravenous drug users), may result in diffuse lung granulomas centered on foreign bodies that are birefringent in polarized light. Recurrent aspiration may lead to airway-centered granulomatous inflammation.

Eosinophilic Pneumonias

Acute Eosinophilic Pneumonia

Acute eosinophilic pneumonia is a rare cause of acute respiratory failure. Patients present with ARDS and eosinophilic infiltration of the lungs. The presentation is often dramatic and leads to severe hypoxia that requires mechanical ventilation. Affected persons are typically young and often have recently begun smoking. The disease has affected military personnel returning from the Middle East. Acute eosinophilic pneumonia responds dramatically to corticosteroids without rebound after discontinued use. Treatment can be short (2 weeks). Pulmonary eosinophilia is common, but peripheral eosinophilia is rare.

Chronic Eosinophilic Pneumonia

Chronic eosinophilic pneumonia manifests much like COP, with recurrent flulike episodes and migratory, peripheral infiltrates (typically described as a "photographic negative of pulmonary edema"). Peripheral eosinophilia is common. Like COP, chronic eosinophilic pneumonia is exquisitely responsive to corticosteroids, and rebound is frequent after discontinuation of treatment.

Other ILDs

Pulmonary Langerhans Cell Histiocytosis

PLCH is a rare cystic lung disease mostly affecting young white smokers. The typical HRCT pattern in PLCH consists of interstitial thickening with upper lobe–predominant irregular cysts and nodules. Spontaneous pneumothoraces are common (in 25% of patients with the systemic variant of the disease, which is more common in children), and patients may have bone involvement and pituitary insufficiency (central diabetes insipidus). The combination of exophthalmos, diabetes insipidus, and lytic bone lesions (often in the skull) is known as Hand-Schüller-Christian disease. Absolute cessation of smoking is mandatory.

Lymphangioleiomyomatosis

LAM is a cystic lung disease that affects women of childbearing age and is sometimes associated with tuberous sclerosis (in up to 20% of patients). It is characterized clinically by a history of recurrent pneumothoraces (in 50%-80% of patients). Hemoptysis (in 30%) and chylothoraces (in 10%-30%) are also common. HRCT typically shows well-defined cysts scattered homogeneously throughout the lungs, without nodules or interstitial fibrosis. Sirolimus is used to slow the rate of disease progression in symptomatic patients who have impaired lung function. For patients with advanced physiologic impairment or disease progression despite treatment with sirolimus, lung transplant is the definitive treatment.

Pulmonary Alveolar Proteinosis

PAP is a rare, idiopathic form of diffuse lung disease characterized by the filling of alveoli with proteinaceous material consisting mostly of phospholipoprotein. Most patients are smokers younger than 50 years, with a male predominance (male to female ratio, 3:1). PAP is suggested by a nonspecific but characteristic alveolar filling pattern seen with HRCT, described as a crazy-paving pattern with airspace consolidation and thickened interlobular septa. The diagnosis is usually indicated by a milky white return of bronchoalveolar lavage fluid or by lung biopsy findings. In addition to smoking cessation, therapy has involved whole-lung lavage and, more recently, trials of granulocyte-macrophage colony-stimulating factor.

KEY FACTS

✓ Sarcoidosis therapy—
  - corticosteroids
  - reserve for severe organ disease (including progressive lung disease)
  - stage I pulmonary sarcoidosis remains stable or resolves spontaneously without treatment in up to 90% of patients

✓ HP—an allergic reaction to organic antigens (molds, grain dusts, pets and birds, and mycobacterial antigens)

✓ PLCH—
  - rare cystic lung disease
  - mostly in young white smokers
  - spontaneous pneumothoraces are common

✓ LAM—
  - cystic lung disease
  - affects women of childbearing age
  - sometimes associated with tuberous sclerosis
  - history of recurrent pneumothoraces

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Obstructive Lung Diseases

VIVEK N. IYER, MD

Overview of Obstructive Lung Diseases

Obstructive lung diseases include chronic obstructive pulmonary disease (COPD) (eg, chronic bronchitis and emphysema), asthma, bronchiectasis, cystic fibrosis, obliterative bronchiolitis, α_1-antitrypsin deficiency, airway stenosis, and diffuse panbronchiolitis. The 2 most prevalent obstructive lung diseases are COPD and asthma.

Asthma is a chronic inflammatory disorder of the airways associated with *reversible* airflow obstruction and airway hyperresponsiveness leading to recurrent episodes of wheezing, dyspnea, chest tightness, and cough; the inflammation is predominantly eosinophilic. **COPD**, in contrast, is characterized by a *persistent* airflow obstruction that is usually progressive and associated with smoking and neutrophilic airway inflammation. **Emphysema** describes a *pathologic* condition of alveolar destruction with centriacinar, panacinar, or bullous emphysema that is visualized on computed tomography of the chest. **Chronic bronchitis** describes a *clinical* condition in which a chronic productive cough is present for at least 3 months for 2 consecutive years. Chronic bronchitis is an independent risk factor for an accelerated worsening of lung function and an increase in mortality and number of hospitalizations. Some patients have an overlap syndrome with elements of both asthma and COPD. Several characteristics are useful for distinguishing these disorders (Table 76.1). Asthma is discussed in Chapter 2 (“Asthma”).

Key Definition

Asthma: *a chronic inflammatory disorder of the airways associated with reversible airflow obstruction and airway hyperresponsiveness leading to recurrent episodes of wheezing, dyspnea, chest tightness, and cough; the inflammation is predominantly eosinophilic.*

Key Definition

Chronic obstructive pulmonary disease: *a persistent airflow obstruction that is usually progressive and associated with smoking and neutrophilic airway inflammation.*

Key Definition

Emphysema: *alveolar destruction with centriacinar, panacinar, or bullous emphysema that is visualized on computed tomography of the chest.*

Key Definition

Chronic bronchitis: *presence of a chronic productive cough for ≥3 months for 2 consecutive years.*

Etiology of COPD

The primary cause of COPD in developed countries is tobacco smoking. Compared with nonsmokers, cigarette smokers have 10 times the risk of dying of COPD. In addition, smoking accelerates the decline of lung function and the development of COPD in persons who have α_1-antitrypsin deficiency. Marijuana smoking has also been associated with bullous emphysema, COPD, and chronic bronchitis–type symptoms. In developing countries, air pollution (both indoor and outdoor) is a major cause of COPD. Occupational and environmental exposures, heredity

Table 76.1 • Characteristic Features That Are Useful for Distinguishing Emphysema, Chronic Bronchitis, and Asthma

Characteristic	Emphysema	Chronic Bronchitis	Asthma
Age at onset	Typically ≥50 y	Typically ≥50 y	Typically childhood and early adulthood (but can also occur in older adults)
Atopy	Absent	Absent	Present
Smoking history	Yes (typically heavy)	Yes (typically heavy)	No
Classic clinical phenotype	Dyspnea in an older adult with a low body mass index and history of smoking (“pink puffer”)	Chronic productive cough with hypoxemia (“blue bloater”)	Episodic wheezing, cough, and chest tightness (both daytime and nocturnal)
Need for supplemental oxygen	Yes	Yes	No
Bronchial hyperresponsiveness (positive methacholine challenge test)	No	No	Yes
Exhaled oral nitric oxide	Normal	Normal	Elevated (≥40 parts per billion)
Variable airflow obstruction (eg, morning peak expiratory flow variability)	No	No	Yes
Diffusing capacity	Decreased	Normal or decreased	Normal
Chest radiography	Hyperinflation (teardrop heart, flattened diaphragm, and hyperinflated lungs with decreased markings)	Increased bronchial markings May show features of hyperinflation as seen in emphysema	Usually normal between acute exacerbations Increased bronchial markings may be seen because of bronchial wall thickening

(α_1-antitrypsin deficiency), and repeated infections (cystic fibrosis and bronchiectasis) are other factors involved in the development of COPD.

α_1-Antitrypsin is a secretory glycoprotein that maintains a balance between proteolytic and antiproteolytic activity in the lung. α_1-Antitrypsin deficiency is inherited in an autosomal codominant fashion. The most common normal phenotype is MM (2 copies of the M allele). Deficient phenotypes are SZ, MZ, ZZ (severe), and null (severe). Patients often present in the third or fourth decade of life with emphysema and have a family history of COPD. Liver disease occurs in up to 10% to 15% of patients. Typically, smoking-related emphysema is predominantly upper lobe and centrilobular, whereas α_1-antitrypsin deficiency–related emphysema is predominantly lower lobe and panacinar.

Causes and Complications of COPD Exacerbations

About half of all COPD exacerbations are caused by viruses. Common bacterial pathogens include *Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae*, and other gram-positive and gram-negative species. COPD exacerbations result in faster functional decline, poorer quality of life, accelerated loss of lung function, and increased mortality. Preventing COPD exacerbations has thus become an essential component of good COPD management, and several strategies have been developed, including the use of combination bronchodilator therapy (details below), azithromycin therapy, and vaccination. Acute COPD exacerbations require treatment with antibiotics, corticosteroids, and bronchodilators; if the exacerbation is severe, hospitalization is required.

Treatment of COPD

COPD outcomes are affected by not only the use of supplemental oxygen and the forced expiratory volume in the first second of expiration (FEV_1) but also by COPD exacerbations, exercise capacity, and symptom burden. As a result, the cornerstone of COPD management involves the accurate assessment and management of these variables: risk factors (eg, smoking cessation), severity of airflow obstruction, frequency of COPD exacerbations, presence of respiratory and nonrespiratory symptoms related to COPD, exercise capacity, and the need for long-term oxygen therapy. Initial steps in managing COPD are outlined in Box 76.1.

Box 76.1 • Initial Steps in Management of COPD

1. Eliminating or addressing causative or exacerbating factors (with a strong emphasis on smoking cessation, including formal counseling and discussion of nicotine replacement strategies and pharmacologic adjuncts to improve quit rates)
2. Ruling out other diagnoses (asthma, bronchiectasis, bronchiolitis, and α_1-antitrypsin deficiency)
3. Assessing the extent of lung impairment (pulmonary function testing and oxygen assessment)
4. Assessing the COPD phenotype (degree of FEV_1 impairment, symptom burden, exercise capacity, and exacerbation frequency)
5. Assessing the need for long-term supplemental oxygen
6. Formulating an inhaler and drug treatment plan
7. Enrolling the patient in a rehabilitation program
8. Educating the patient and family on inhaler technique and the disease

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second of expiration.

KEY FACTS

✓ COPD—

- tobacco smoking is the primary cause in developed countries
- risk of dying of COPD is 10 times higher for cigarette smokers than for nonsmokers
- patients often present in third or fourth decade of life with chronic bronchitis or emphysema (or both) and family history of COPD
- smoking-related emphysema: usually upper lobe predominant and centrilobular
- α_1-antitrypsin deficiency–related emphysema: predominantly lower lobe and panacinar
- assessment includes exercise capacity, exacerbation frequency, symptoms, and pulmonary function
- number of COPD exacerbations and hospitalizations increases with worsening obstruction (and lower FEV_1)

✓ Treatment of COPD—

- assessment of mitigation of risk factors (eg, smoking cessation)
- LTOT is recommended if Pao_2 ≤55 mm Hg (ie, Spo_2 ≤88%)
- selection of appropriate bronchodilators according to the patient's GOLD group and exacerbation history
- for acute exacerbations: antibiotics, oral corticosteroids, and bronchodilators

Risk Factors

Given that smoking is the preeminent risk factor in the development and progression of COPD, smoking cessation should be discussed and programs offered to all current smokers. Decreased exposure to household air pollution, occupational dusts, gases, and fumes and other pollutants is also important in the management of COPD.

Oxygen

Long-term oxygen therapy (LTOT) (≥15 hours daily) decreases mortality among COPD patients and is approved and recommended when the Pao_2 is 55 mm Hg or less (corresponding to oxygen saturation as measured by pulse oximetry [Spo_2] ≤88%). If a patient has clinical evidence of cor pulmonale, congestive heart failure, or polycythemia, LTOT can be started at a higher Pao_2 (56-59 mm Hg), but the use of LTOT is not associated with a mortality benefit for patients who have a Pao_2 of 56 to 59 mm Hg without evidence of cor pulmonale, congestive heart failure, or polycythemia. With LTOT, the target Spo_2 should be at least 90%. Nocturnal oxygen is typically prescribed at a flow rate that is 1 L/min higher than the daytime resting oxygen requirement. When patients have cor pulmonale or suspected sleep apnea, a polysomnogram or nocturnal pulse oximetry may be useful to exclude sleep apnea and to document adequate nocturnal oxygenation (Spo_2 ≥0%). The need for oxygen therapy long-term or indefinitely should be reassessed after 3 months of treatment. Exercise therapy (ie, pulmonary rehabilitation) improves exercise tolerance and maximal oxygen uptake but does not improve spirometry values.

Assessment of COPD

The first report of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) was published in 2001 with major revisions in 2006, 2011, and 2017. The most recent iteration is shown in Figure 76.1. This framework facilitates a comprehensive, multidimensional COPD assessment, including number of exacerbations, exercise capacity, respiratory symptoms, and spirometry values.

Bronchodilators

Bronchodilator drugs are administered to reverse bronchoconstriction (bronchospasm). Proper inhalation technique is essential to ensure optimal outcomes. Commonly used

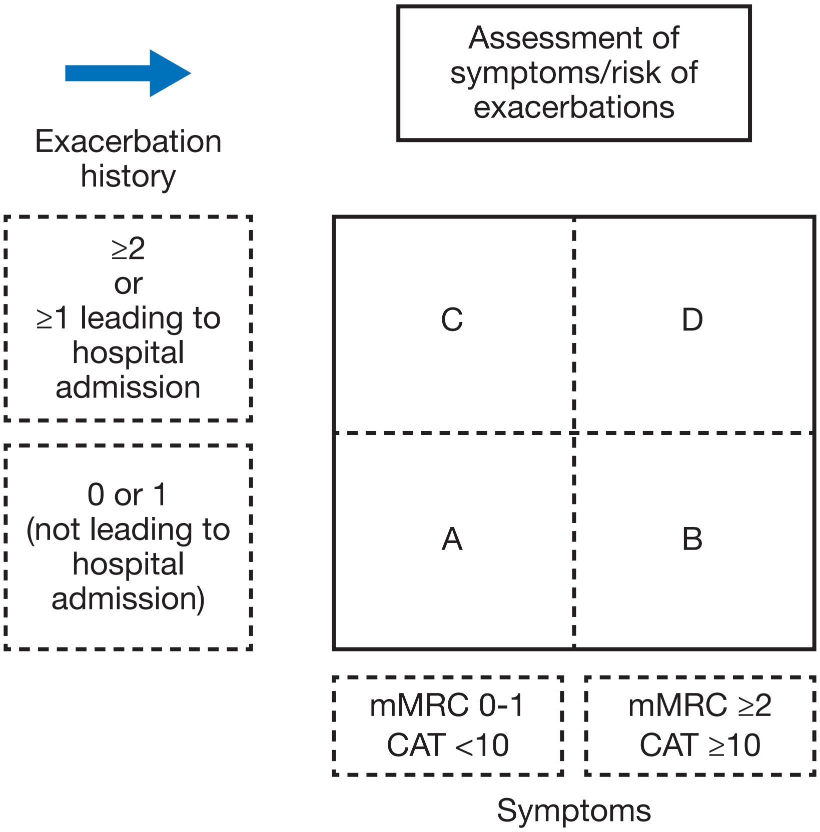
Assessment of symptoms/risk of exacerbations
Exacerbation history
≥2 or ≥1 leading to hospital admission
0 or 1 (not leading to hospital admission)
C
D
A
B
mMRC 0-1 CAT <10
mMRC ≥2 CAT ≥10
Symptoms

Figure 76.1. *Chronic Obstructive Pulmonary Disease (COPD) Grouping According to the ABCD Assessment Tool of the Global Initiative for Chronic Obstructive Lung Disease (GOLD). CAT indicates COPD Assessment Test; mMRC, modified British Medical Research Council questionnaire.*

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bronchodilators include 1) short-acting β-adrenergic agonists (eg, albuterol, isoproterenol, levalbuterol, metaproterenol, and pirbuterol) or long-acting β-adrenergic agonists (LABAs) (eg, salmeterol, formoterol, vilanterol, indacaterol, olodaterol, and arformoterol) and 2) short-acting muscarinic antagonists (eg, ipratropium and oxitropium) or long-acting muscarinic antagonists (LAMAs) (eg, tiotropium, aclidinium, umeclidinium, and glycopyrronium). In addition, several new long-acting LABAs and LAMAs are in development.

Short-Acting β-Adrenergic (β_2-Selective) Agonists

Short-acting β-adrenergic agonists are the most commonly used bronchodilators. In most patients, single doses of these agents produce clinically important bronchodilation within 5 minutes (peak effect occurs 30-60 minutes after inhalation, with a beneficial effect lasting 3-4 hours). The dosage should be tailored on the basis of clinical features and potential side effects. Adverse effects, including tremor, anxiety, restlessness, tachycardia, palpitations, increased blood pressure, and cardiac arrhythmias, are more likely in patients who have cardiovascular, liver, or neurologic disorders and in elderly patients. Rarely, paradoxical bronchospasm results from tachyphylaxis (a rapidly decreasing response to a drug after a few doses) or from exposure to preservatives and propellants. A newer, single-isomer β-agonist, levalbuterol, binds to β-adrenergic receptors with a 100-fold greater affinity than albuterol. Metered dose inhalers are just as effective as nebulized medications, but the total dose of medication is higher in the nebulized formulation.

Long-Acting β-Adrenergic (β_2-Selective) Agonists

Single-agent LABAs (or LAMAs) are currently recommended for patients in GOLD group B. Salmeterol is highly lipophilic (albuterol is hydrophilic); hence, it has a depot effect in tissues. Salmeterol has a prolonged duration of action (10-12 hours) and inhibits the release of proinflammatory and spasmogenic mediators from respiratory cells. Salmeterol and formoterol are also effective in preventing exercise-induced asthma, methacholine-induced bronchospasm, and allergen challenge. Adverse effects are similar to those of other β-adrenergic agents. Other LABAs with similar properties include vilanterol, olodaterol, and indacaterol.

Anticholinergic Agents

Short-acting anticholinergic agents are useful for achieving immediate bronchodilation. As a single agent, ipratropium is only modestly effective: It prevents bronchoconstriction caused by cholinergic agents, but it does not provide complete protection against bronchoconstriction produced by tobacco smoke, citric acid, sulfur dioxide, or carbon dust. Ipratropium does not cross the blood-brain barrier, and it can aggravate narrow-angle glaucoma and bladder outflow obstruction.

Tiotropium is a long-acting, once-daily, inhaled anticholinergic (a LAMA) that provides prolonged bronchodilation in patients with COPD. Because tiotropium decreases the

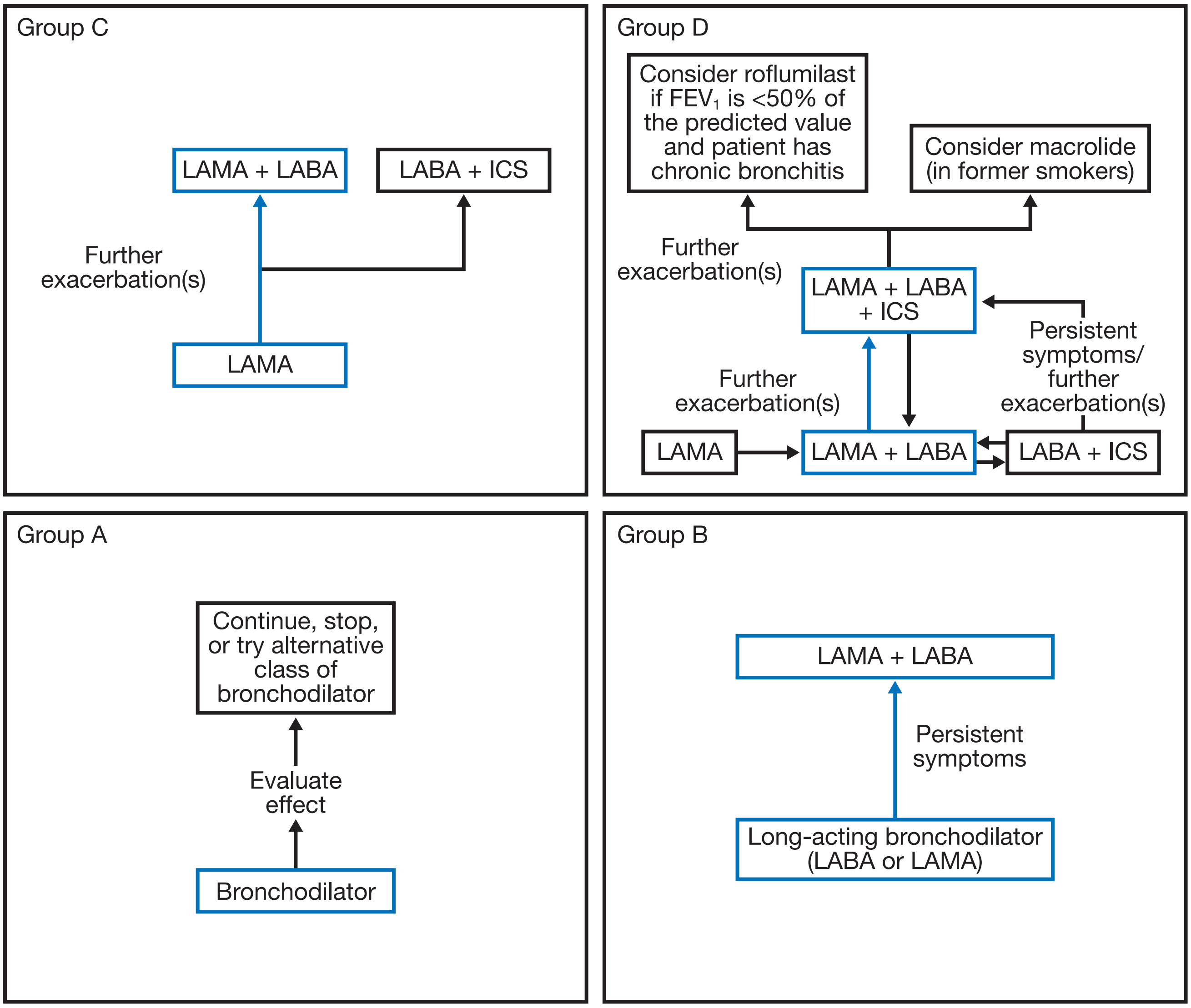
Group C
LAMA + LABA
LABA + ICS
Further exacerbation(s)
LAMA
Group D
Consider roflumilast if FEV1 is <50% of the predicted value and patient has chronic bronchitis
Consider macrolide (in former smokers)
Further exacerbation(s)
LAMA + LABA + ICS
Persistent symptoms/ further exacerbation(s)
Further exacerbation(s)
LAMA
LAMA + LABA
LABA + ICS
Group A
Continue, stop, or try alternative class of bronchodilator
Evaluate effect
Bronchodilator
Group B
LAMA + LABA
Persistent symptoms
Long-acting bronchodilator (LABA or LAMA)

Figure 76.2. *Therapy for Chronic Obstructive Pulmonary Disease According to the ABCD Grouping of the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Blue boxes and arrows indicate preferred treatment pathways. FEV_1 indicates forced expiratory volume in the first second of expiration; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist.* (Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. Am J Respir Crit Care Med. 2017 Mar 1;195(5):557-82. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.)

frequency of exacerbations, it is superior to single-agent LABAs in this regard. It also provides bronchodilation and improves symptoms, but it does not alter the course of lung function decline in patients with COPD. Other LAMAs (glycopyrronium, aclidinium, and umeclidinium) appear to have similar properties.

Phosphodiesterase Inhibitors

The use of theophylline (a nonspecific phosphodiesterase inhibitor) has greatly diminished with the availability of various inhaled bronchodilators. Theophylline has a narrow therapeutic window and a wide range of toxic effects (eg, cardiac arrhythmias and grand mal seizures), and it interacts with other drugs. Roflumilast is a long-acting, selective phosphodiesterase-4 inhibitor that has shown modest benefit in reducing the exacerbation risk for patients with COPD and the chronic bronchitis phenotype.

Corticosteroids (Oral and Inhaled)

A short course of systemic corticosteroids serves as a useful adjunct in the treatment of acute COPD exacerbation by reducing the duration and severity of the illness. A short course (5 days) of oral prednisone (40 mg) may have the same efficacy as a longer course (10 days). Inhaled corticosteroids (ICSs) do not slow the worsening of lung function or affect mortality in COPD, but they may decrease the frequency of exacerbations and modestly improve COPD symptoms. The use of ICSs has also been associated with an increased risk of pneumonia.

Combination Therapy

Recent studies have confirmed that the preferred first-line therapy for most patients with COPD is the use of a LABA in combination with a LAMA (Figure 76.2). This combination appears to have superior efficacy over a LABA-ICS combination for decreasing COPD exacerbation rates. In addition, a LABA-LAMA combination is superior to either medication alone for improving bronchodilation and reducing COPD symptoms. Similarly, studies have confirmed that a triple combination (LABA-LAMA-ICS) therapy is superior to LABA-ICS therapy for reducing the frequency of COPD exacerbations, improving symptoms, and improving bronchodilation. Triple combination therapy is appropriate for severe COPD with frequent exacerbations (Figure 76.2) and is currently used in about 25% of patients with COPD in the United States according to a large claims-based database study.

Adjuvant Therapy

Long-term azithromycin therapy is beneficial in patients with frequent COPD exacerbations (≥2 per year). Antibiotic therapy is helpful for patients with symptoms suggestive of an acute bacterial infection, especially during COPD exacerbations. Maintenance of good oral hydration, avoidance of tobacco smoking and other respiratory irritants, pneumococcal vaccination, annual influenza vaccination, and prompt treatment of respiratory infections are equally important. Supervised COPD disease management programs have shown mixed benefit for decreasing the number of emergency department visits or COPD-related hospitalizations.

Lung Volume Reduction

Surgical and bronchoscopic techniques are available to decrease the volume of poorly functioning emphysematous areas in patients with severe COPD. Lung volume reduction surgery has been shown to improve exercise capacity, quality of life, and survival of patients who have heterogeneous emphysema and poor baseline exercise capacity. Referral to a center with expertise in COPD evaluation is recommended when considering these options.

KEY FACTS

✓ Tiotropium for COPD—
  - decreases exacerbation frequency
  - provides bronchodilation
  - improves symptoms
  - does not stop the worsening of lung function

✓ Systemic corticosteroids for COPD—adjunct treatment of acute exacerbation; reduce duration and severity of illness

✓ ICSs for COPD—
  - do not slow the worsening of lung function
  - do not affect mortality
  - may decrease frequency of exacerbations
  - may modestly improve symptoms
  - may increase risk of pneumonia

✓ Adjuvant therapy for COPD—
  - long-term azithromycin therapy for frequent exacerbations (≥2 per year)
  - good oral hydration
  - avoidance of tobacco smoking and other respiratory irritants
  - pneumococcal vaccination and annual influenza vaccination
  - prompt treatment of respiratory infections

✓ Lung volume reduction surgery for COPD—improves exercise capacity, quality of life, and survival of patients with heterogeneous emphysema and poor baseline exercise capacity

77 Pulmonary Evaluation

VIVEK N. IYER, MD

Symptoms and Signs

Cough

Cough is one of the most common reasons for outpatient medical consultation. Cough can be classified according to duration as *acute* (<3 weeks), *subacute* (3-8 weeks), and *chronic* (>8 weeks). Acute cough is usually related to an infectious cause, and symptomatic management usually suffices. Chronic cough, in contrast, is mainly related to postnasal drip, asthma, or gastroesophageal reflux disease. Angiotensin-converting enzyme inhibitors have been implicated in up to 10% of patients with chronic cough. In about 50% of patients, chronic cough is due to more than 1 cause. For patients with chronic cough, the specific characteristics of the cough (eg, timing, character, and productive or not productive) do not seem to correlate with the underlying cause.

Hemoptysis

Hemoptysis is the expectoration of blood originating from the lower respiratory tract. Bleeding from the upper airways (ie, the nose, mouth, pharynx, and larynx) and the gastrointestinal tract often resembles hemoptysis, but the clinical history can be helpful for differentiation. The pulmonary parenchyma and airways are supplied by pulmonary arteries and bronchial arteries. Causes of hemoptysis can be broadly divided into airway causes (eg, bronchitis, bronchiectasis, neoplasms, foreign body, and trauma); pulmonary parenchymal causes (eg, Goodpasture syndrome, pulmonary vasculitis, and lung infections); and pulmonary vascular causes (eg, pulmonary embolism, pulmonary arteriovenous malformations, and mitral stenosis).

Key Definition

Hemoptysis: ***expectoration of blood originating from the lower respiratory tract.***

Dyspnea

Dyspnea is a uniquely human phenomenon. This term is used to characterize a subjective experience of breathing discomfort consisting of qualitatively distinct sensations that vary in intensity. Patients use many terms to describe their subjective sense of dyspnea (eg, *air hunger, starved for air, unsatisfied inspiration, heavy breathing, feelings of chest constriction, rapid breathing, inability to fully inspire or expire, increased work of breathing*, and *sense of suffocation*).

Dyspnea occurs when the cerebral cortex or brainstem perceives a suboptimal degree of lung stretch (through afferent signals from mechanoceptors in the lung, airway, and chest wall) for the given intensity of the ventilatory drive. Dyspnea can be acute or chronic and requires a thorough workup based on the clinical context to exclude pathology that may be cardiac (myocardial, valvular, and pericardial); pulmonary (parenchymal, vascular, and chest wall or pleural); or neuromuscular. The workup should include comprehensive neurologic and cardiopulmonary examinations. Additional diagnostic evaluation may include echocardiography; pulmonary function tests (PFTs) (including maximal respiratory pressure assessment); computed tomography (CT) of the chest; and oxygen assessment (at rest and with exercise). The US Food and Drug Administration has not approved drugs specifically for dyspnea, but opioids are the most commonly prescribed class of medications that decrease the respiratory drive at both the brainstem and the cortex.

History and Examination

An approach to the history and physical examination of patients with pulmonary disease is outlined in Box 77.1. Percussion and auscultation findings associated with various pulmonary conditions are listed in Table 77.1.

Box 77.1 • History and Physical Examination of Patients With Pulmonary Disease

- History
  - Smoking
  - Occupational exposure
  - Exposure to infected persons or animals
  - Hobbies and pets
  - Family history of diseases of the lung and other organs
  - Past malignancy
  - Systemic (nonpulmonary) diseases
  - Immune status (corticosteroid therapy, chemotherapy, cancer)
  - History of trauma
  - Previous chest radiography
- Examination
  - Inspection
    - Respiratory rate, hoarseness
    - Respiratory rhythm (abnormal breathing pattern)
    - Accessory muscles in action (FEV_1 <30%)
    - Postural dyspnea (orthopnea, platypnea, trepopnea)
    - Intercostal retraction
    - Paradoxical motions of abdomen or diaphragm
    - Cough (type, sputum, blood)
    - Wheeze (audible with or without stethoscope)
    - Pursed lip breathing or glottic wheeze (patients with COPD)
    - Cyanosis (central vs peripheral)
    - Conjunctival suffusion (CO_2 retention)
    - Clubbing
    - Thoracic cage (eg, anteroposterior diameter, kyphoscoliosis, pectus carinatum)
    - Trachea, tracheal deviation
    - Superior vena cava syndrome
  - Asterixis, central nervous system status
  - Cardiac impulse, jugular venous pressure, pedal edema (signs of cor pulmonale)
- Palpation
  - Clubbing
  - Lymphadenopathy
  - Tibial tenderness (hypertrophic pulmonary osteoarthropathy)
  - Motion of thoracic cage (hand or tape measure)
  - Chest wall tenderness (costochondritis, rib fracture, pulmonary embolism)
  - Tracheal deviation or tenderness, tactile (vocal) fremitus
  - Subcutaneous emphysema
  - Succussion splash (effusion; air-fluid level in thorax)
- Percussion
  - Thoracic cage (dullness, resonance)
  - Diaphragmatic motion (normal, 5-7 cm)
  - Upper abdomen (liver)
- Auscultation
  - Tracheal auscultation
  - Normal breath sounds
  - Bronchial breath sounds
  - Expiratory slowing
  - Crackles
  - Wheezes
  - Pleural rub
  - Mediastinal noises (mediastinal crunch)
  - Heart sounds
  - Miscellaneous (muscle tremor, etc)

Abbreviations: CO_2, carbon dioxide; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second of expiration.

Diagnostic Tests

Plain Chest Radiography

The ability to identify normal radiographic anatomy of the chest is essential. A step-by-step method should be used to interpret chest radiographs so that subtle abnormalities are not missed (Box 77.2).

Initially, the chest radiograph should be assessed overall without focusing on any specific area or abnormality. Then the evaluation should continue with the extrathoracic structures and move inward. For example, destructive shoulder arthritis may indicate rheumatoid arthritis and prompt a search for associated pulmonary manifestations; the absence of a breast shadow in a female patient should prompt evaluation for signs of pulmonary metastases of breast cancer; visualization of a tracheostomy stoma or cannula may indicate previous laryngeal cancer (suggesting the possibility of complications such as aspiration pneumonia and lung metastases); and the cause of a pleuropulmonary process may be indicated by infradiaphragmatic abnormalities (eg, calcifications in the spleen, displacement of the gastric bubble and colon, and signs of upper abdominal surgery).

The skeletal thorax should be viewed next to exclude rib fractures, osteolytic and other lesions of the ribs, rib notching,

Table 77.1 • Percussion and Auscultation Findings in Pulmonary Conditions

Condition	Chest Expansion	Fremitus	Resonance	Breath Sounds	Egophony[a]	Bronchophony[a]
Pleural effusion[b]	Decreased	Decreased	Decreased	Decreased	Absent >> present	Absent >> present
Consolidation[c]	Decreased	Increased	Decreased	Bronchial	Present	Present
Atelectasis[d]	Decreased	Decreased	Decreased	Decreased	Absent > present	Absent > present
Pneumothorax	Variable	Decreased	Increased	Decreased	Absent	Absent

[a] Inequality signs indicate *more often than* (>) or *much more often than* (>>).
[b] The trachea is shifted contralaterally in effusion.
[c] Whispered pectoriloquy is present in consolidation.
[d] The trachea is shifted ipsilaterally in atelectasis.

Box 77.2 • Systematic Approach for Evaluating a Chest Radiograph

1. Examination for patient identifier
2. Evaluation of the extrathoracic structures (eg, for evidence of destructive arthritis, the absence of a breast shadow, or a tracheostomy stoma)
3. Evaluation for infradiaphragmatic abnormalities
4. Assessment for skeletal changes (eg, rib fractures, notching, osteolytic lesions, or sternal wires)
5. Evaluation of intrathoracic but extrapulmonary structures and features (eg, mediastinum, thyroid calcification, achalasia, aortopulmonary window, hila, and calcified adenopathy)
6. Evaluation of the pleural surfaces (eg, for blunting or calcification)
7. Evaluation of the pulmonary parenchyma (eg, for infiltrates, air bronchogram, nodules, cysts, abscess, or pneumothorax)
8. Evaluation of the retrocardiac and retrodiaphragmatic spaces on lateral views

missing ribs, and vertebral abnormalities. Changes due to previous thoracic surgical procedures (eg, coronary artery bypass, thoracotomy, lung resection, or esophageal surgery) may provide clues to the pulmonary disease.

Assessment should then focus on the intrathoracic but extrapulmonary structures, such as the mediastinum (including the great vessels, esophagus, heart, lymph nodes, and thymus). A calcified mass in the region of the thyroid almost always indicates a goiter. An obliterated aortopulmonary window (a notch below the aortic knob on the left, just above the pulmonary artery) may indicate a tumor or lymphadenopathy. Right paratracheal and paramediastinal lymphadenopathy can be subtle. Hilar regions are difficult to interpret because lymphadenopathy, vascular prominence, or tumor may make the hila appear larger. The retrocardiac region may show hiatal hernia with an air-fluid level; this may be helpful in the diagnosis of reflux or aspiration.

The pleural regions should be examined for pleural effusion, pleural thickening (particularly in the apices), blunting of the costophrenic angles, pleural plaques or masses, and pneumothorax. A lateral decubitus radiograph may be necessary to confirm the presence of free fluid in the pleural space. An air bronchogram depicting the major airways may indicate a large tumor (by an abrupt cutoff of the air bronchogram) or consolidation from an infection.

The final step is to evaluate the lung parenchyma. Notably, about 15% of the pulmonary parenchyma is located behind the heart and diaphragm; a lateral chest radiograph is helpful in examining this region for retrocardiac or retrodiaphragamatic abnormalities. Increased interstitial lung markings should not be overinterpreted. Generally, bronchovascular markings should be visible throughout the lung parenchyma. The absence of any markings within the lung parenchyma suggests a bulla or an air-containing cyst. Apical areas should be evaluated carefully for the presence of pleural thickening, pneumothorax, small nodules, and subtle infiltrates.

KEY FACTS

✓ Causes of chronic cough—

- postnasal drip
- asthma
- gastroesophageal reflux disease
- angiotensin-converting enzyme inhibitors (10% of patients)
- multiple causes (50% of patients)

✓ Interpretation of chest radiographs—a step-by-step method should be used to avoid missing subtle abnormalities

Common radiographic abnormalities of the chest are depicted in Figures 77.1.

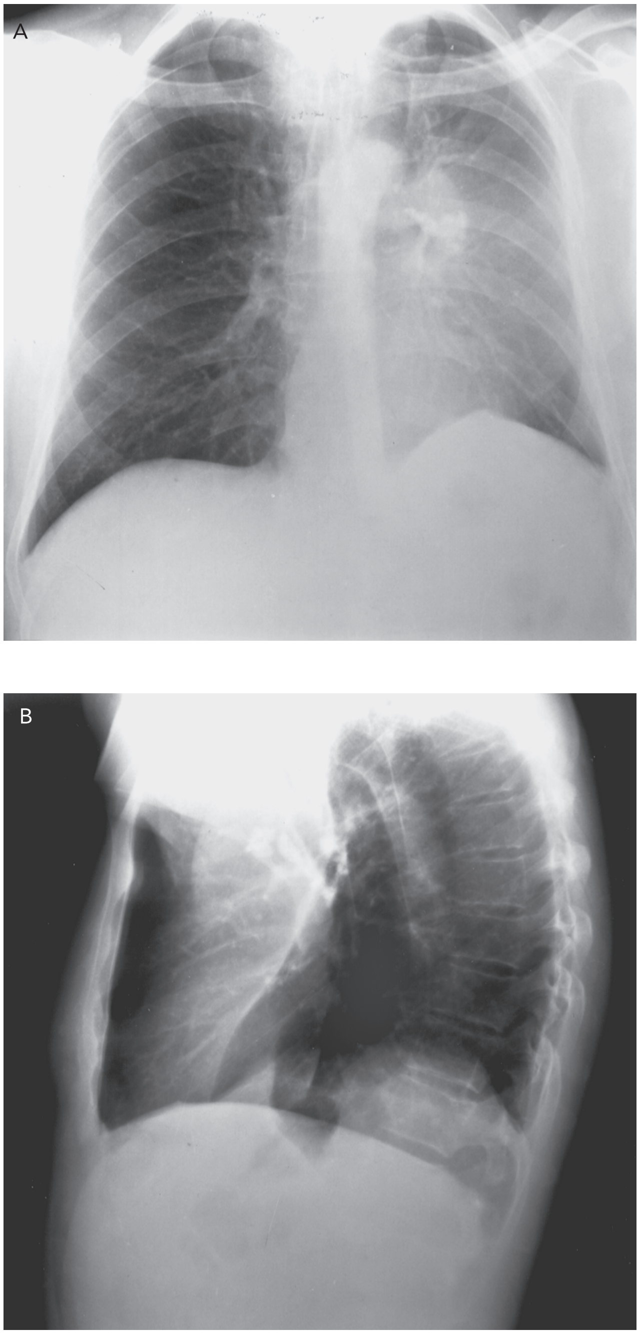

Figure 77.1. *Collapsed Left Upper Lobe. A, Posteroanterior chest radiograph (CXR). B, Lateral CXR. The ground-glass haze over the left hemithorax is typical of a partially collapsed left upper lobe. In more than 50% of patients with collapsed lobes, loss of volume is evidenced by left hemidiaphragmatic elevation; the mediastinum is shifted to the left and the left hilum is pulled cranially. Also, the left main bronchus deviates cranially. Calcification in the left hilar mass is the result of an unrelated, old granulomatous infection. In panel B, the density from the left hilum down toward the anterior portion of the chest is the result of the partially collapsed left upper lobe. The substernal radiolucency is the right lung.*

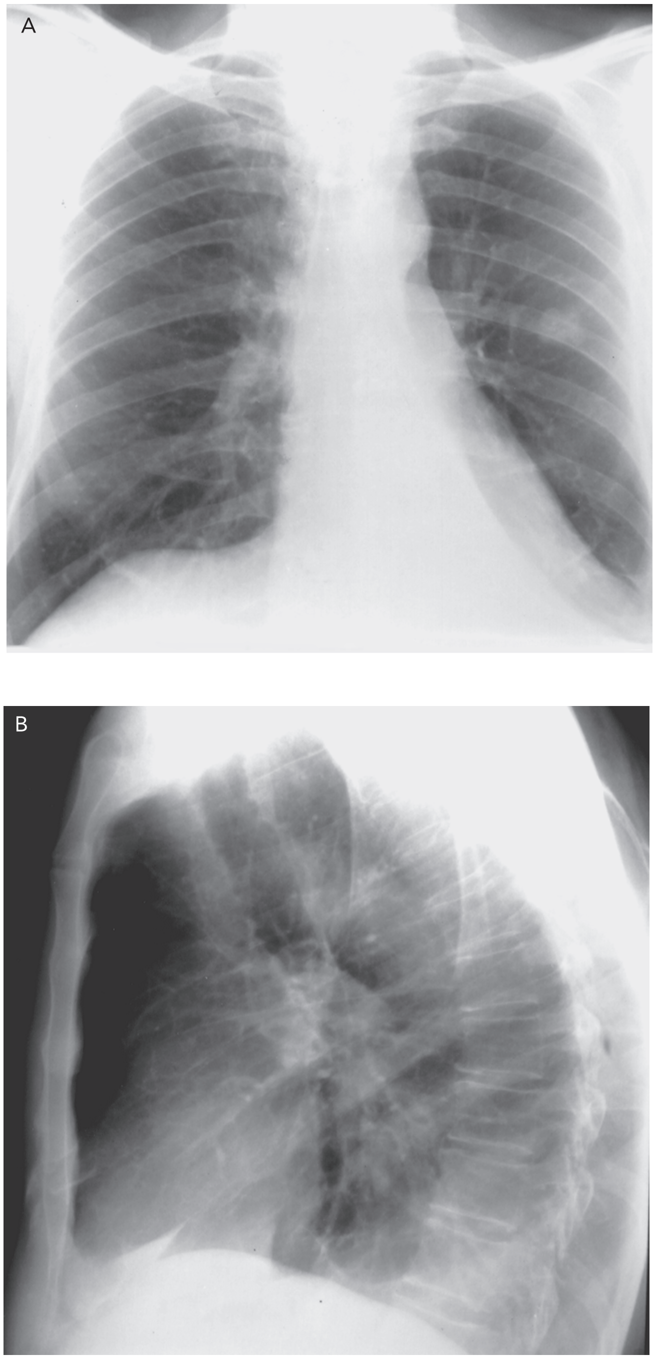

Figure 77.2. *Collapsed Left Lower Lobe. A, Posteroanterior chest radiograph (CXR). B, Lateral CXR. The nodule in the left midlung field and the collapsed left lower lobe (appearing as a density behind the heart) resulted from 2 separate primary lung cancers, which were synchronous bronchogenic carcinomas. Identification of the first evident abnormality, such as the nodule in the midlung field, should not prevent careful evaluation of all other areas. Panel B shows an increased density over the lower thoracic vertebrae without an obvious wedge-shaped infiltrate. Over the anterior portion of the hemidiaphragm, the small wedge-shaped infiltrate is not fluid in the left major fissure because the left major fissure is pulled away posteriorly. Instead, it is an incidental normal variant of fat pushed up into the right major fissure.*

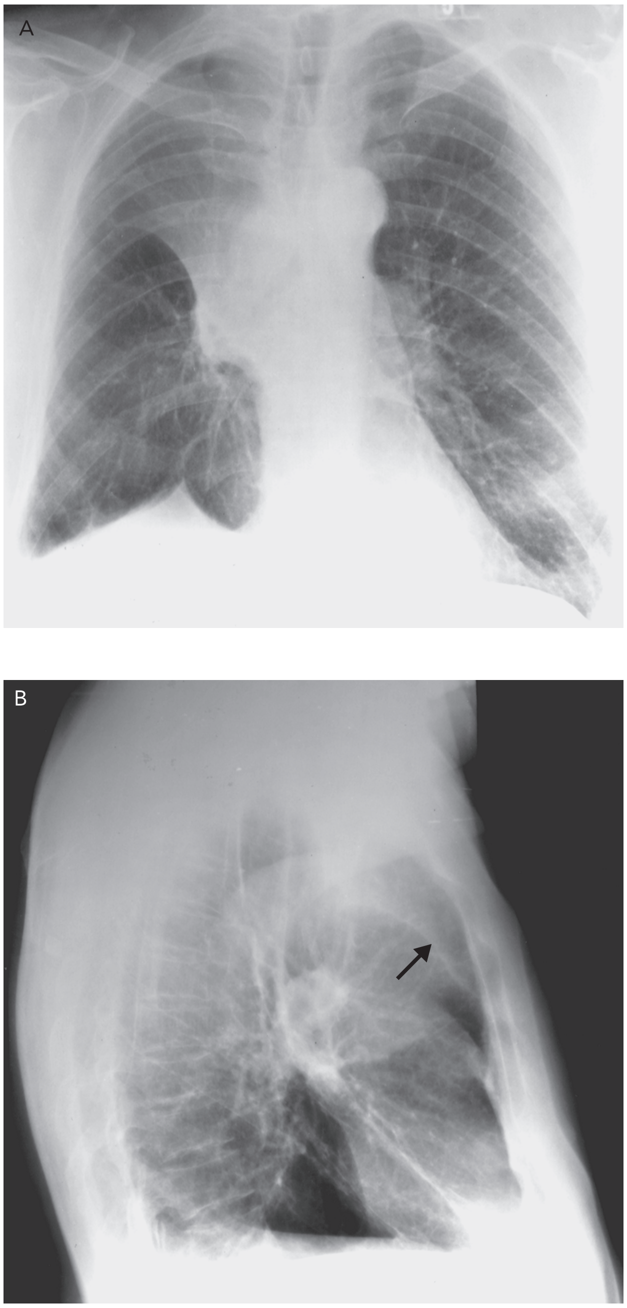

Figure 77.3. *Collapsed Right Upper Lobe. A, Posteroanterior chest radiograph (CXR). B, Lateral CXR. Panel A shows a classic "reversed S" mass in the right hilus with partial collapse of the right upper lobe. Loss of volume is evident with the elevation of the right hemidiaphragm. In panel B, the partially collapsed right upper lobe is faintly seen in the upper anterior portion of the hemithorax (arrow).*

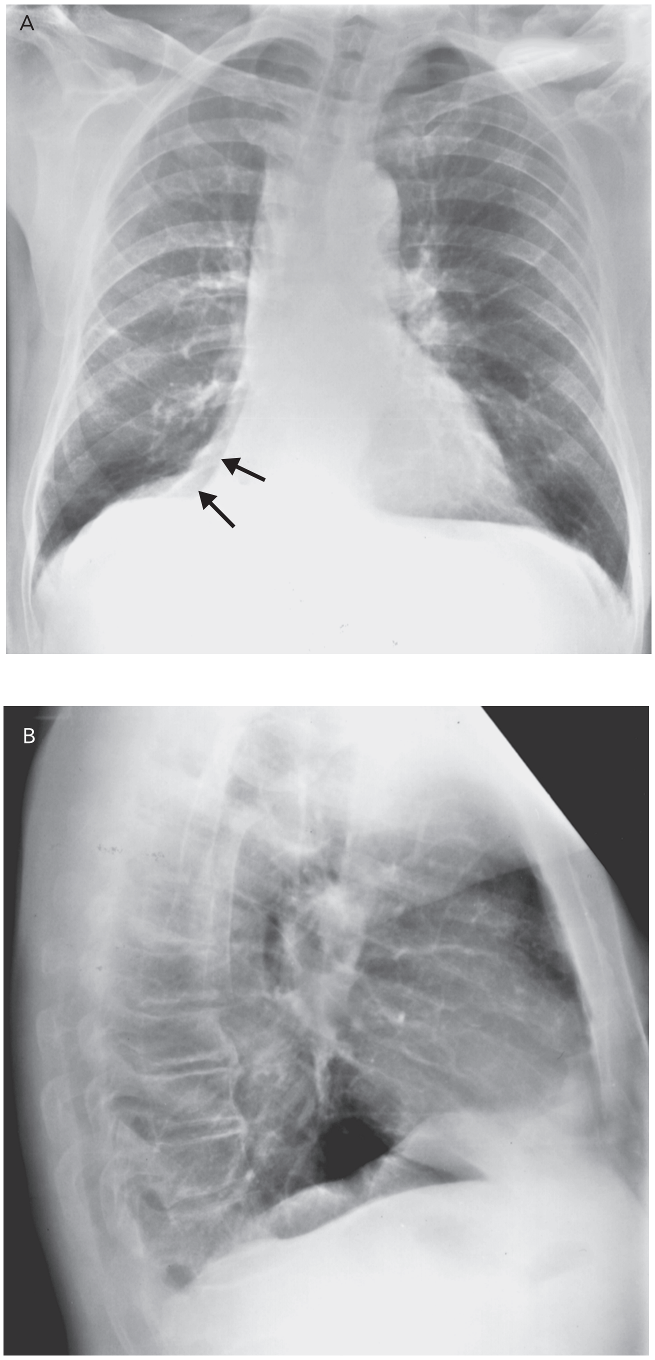

Figure 77.4. *Collapsed Right Lower Lobe. A, Posteroanterior chest radiograph (CXR). B, Lateral CXR. This 75-year-old male smoker had hemoptysis for 1.5 years; his CXR had been read as normal on several occasions. In panel A, the linear density (arrows) projecting downward and laterally along the right border of the heart projects below the diaphragm and is not a normal line. Also, the right hilum is not evident; it has been pulled centrally and downward because of carcinoma obstructing the bronchus of the right lower lobe. The very slight shift in the mediastinum to the right indicates loss of volume. In panel B, the notable collapse of the right lower lobe is indicated by only a subtle, increased density over the lower thoracic vertebrae.*

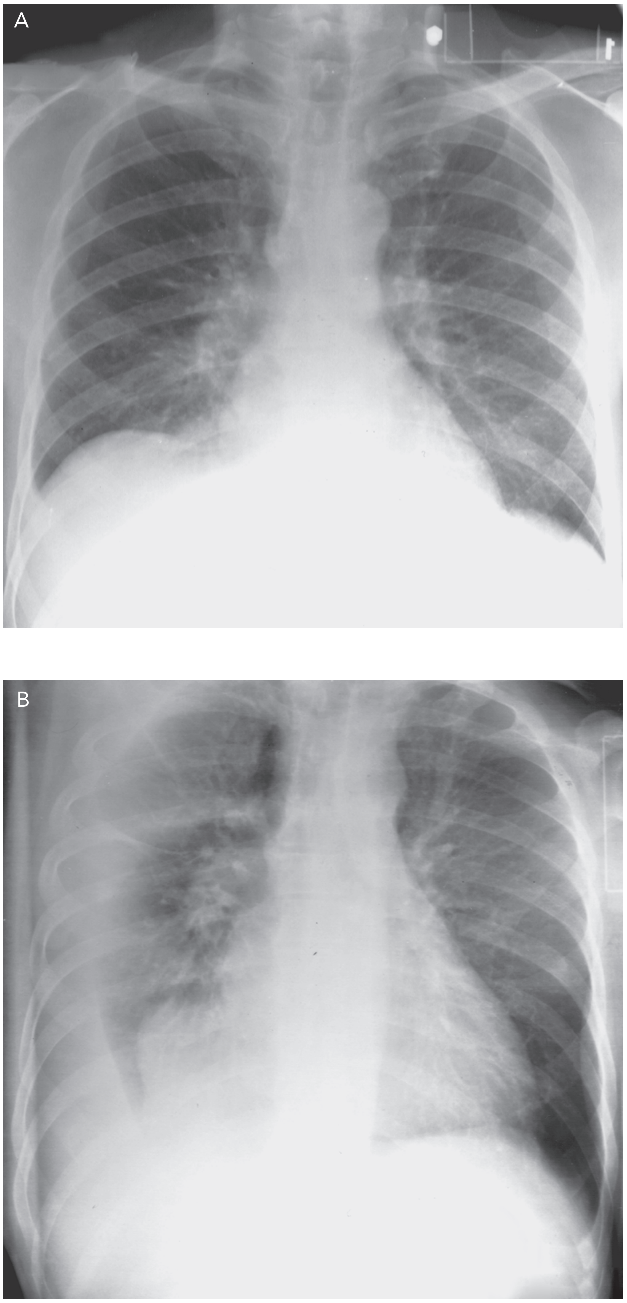

Figure 77.5. *Effusion. A, Posteroanterior chest radiograph (CXR). B, Decubitus CXR. In panel A, an "elevated right hemidiaphragm" is actually an infrapulmonic (or subpulmonic) effusion, as seen in panel B. For unknown reasons, a meniscus is not formed in some people with infrapulmonic pleural effusion. Thus, a seemingly elevated hemidiaphragm should be examined with the suspicion that it could be infrapulmonic effusion. Subpulmonic effusion occurs more frequently in patients with nephrotic syndrome. Decubitus CXR or ultrasonography would disclose the free fluid.*

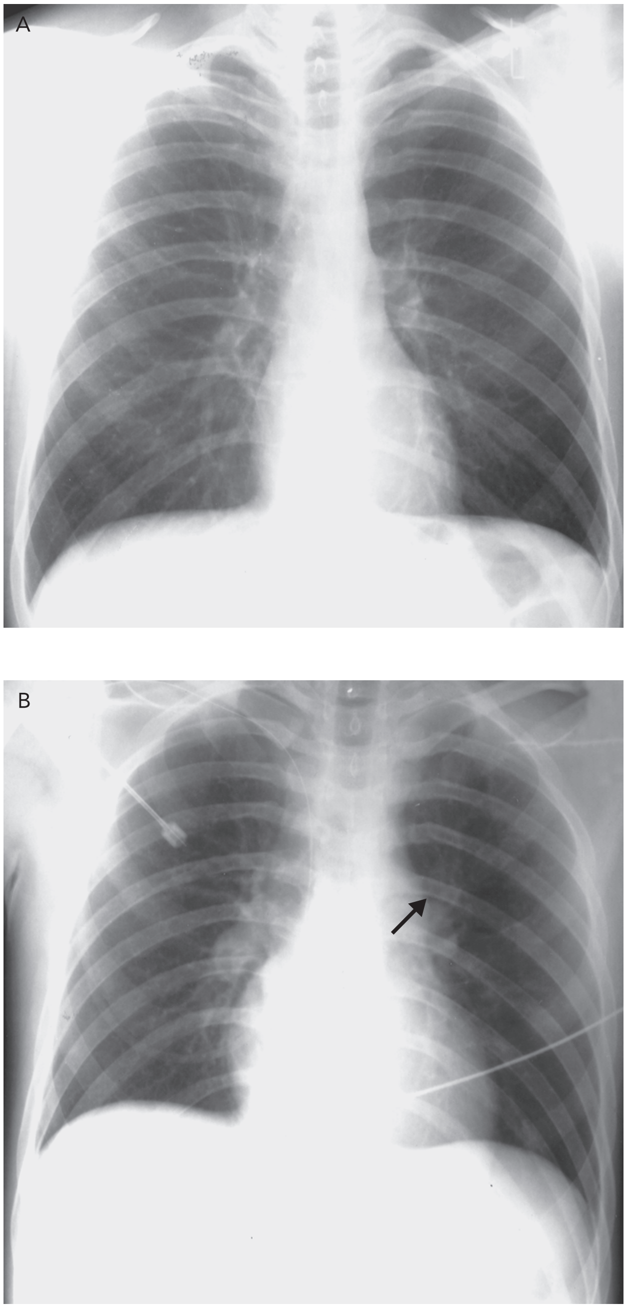

Figure 77.6. *Embolism. A, Prepulmonary embolism on a "normal" posteroanterior chest radiograph (CXR). B, Pulmonary embolism. The CXR is read as normal in up to 30% of patients with angiographically proven pulmonary embolism. In comparison with panel A, panel B shows a subtle elevation of the right hemidiaphragm. In panel A, the right and left hemidiaphragms are equal. In some series, an elevated hemidiaphragm is the most common finding with acute pulmonary embolism. Additional features are the plumpness of the right pulmonary artery, the prominent pulmonary outflow tract on the left (arrow in panel B), and a subtle change in the cardiac diameter. The patient was a 28-year-old man who was in shock from massive pulmonary emboli as a result of major soft tissue trauma from a motorcycle accident 7 days earlier.*

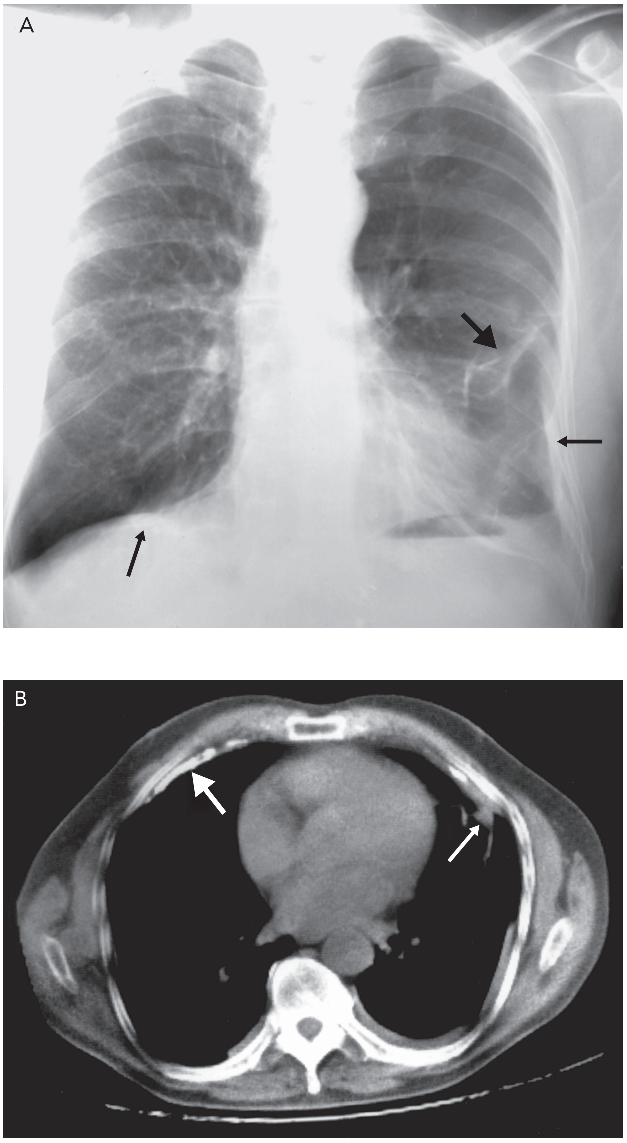

Figure 77.7. *Asbestos Exposure. The patient was a 68-year-old asymptomatic man who smoked. A, Abnormal chest radiograph shows areas of pleural calcification (small arrows), particularly on the right hemidiaphragm. This is a tip-off to previous asbestos exposure. The process in the left midlung was worrisome (large arrow), perhaps indicating a new process such as bronchogenic carcinoma. B, Computed tomography disclosed rounded atelectasis (small arrow). The "comma" extending from this mass is characteristic of rounded atelectasis, which is the result of subacute to chronic pleural effusion resolving and trapping lung as it heals. Pleural calcification is apparent (large arrow).*

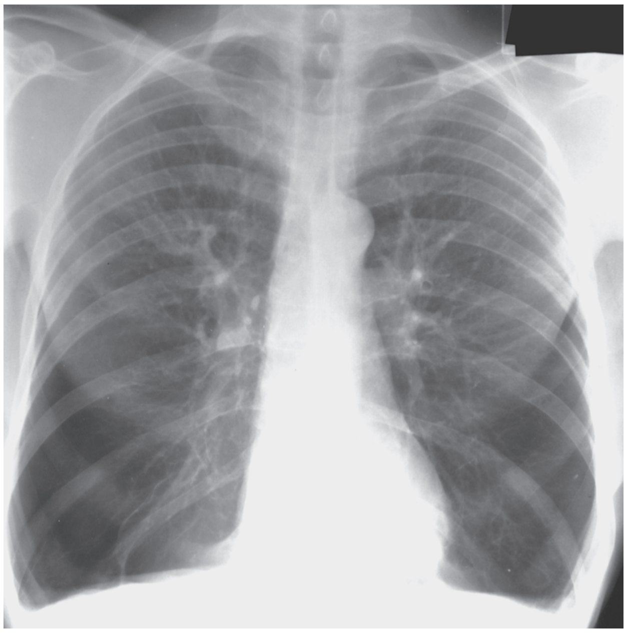

Figure 77.8. *Panlobular Emphysema at the Bases Consistent With the Diagnosis of* α_1*-Antitrypsin Deficiency. Emphysema should not be read into a chest radiograph because all it usually represents is hyperinflation that can occur with severe asthma as well. However, diminished interstitial markings are at the bases with radiolucency. Also, blood flow is increased to the upper lobes because that is where most of the viable lung tissue is.*

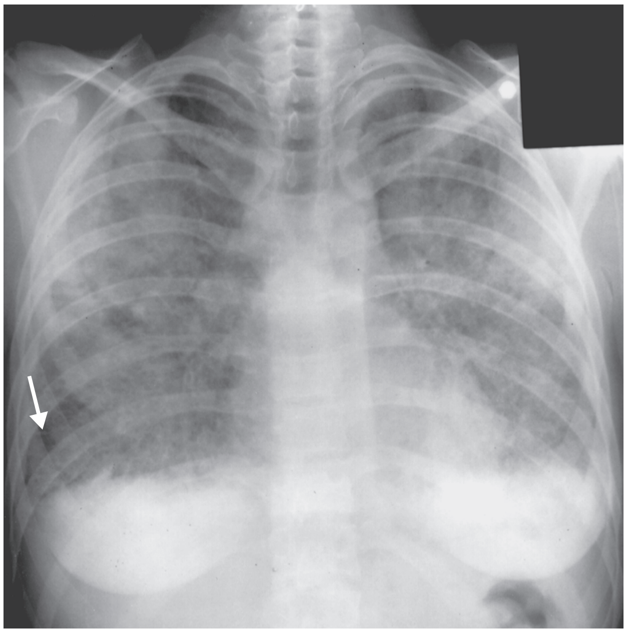

Figure 77.9. *Lymphangitic Carcinoma in a 27-Year-Old Woman. This patient had a 6-week history of progressive dyspnea and weight loss. Because of her young age, neoplasm may not be considered initially. However, the chest radiographic features suggest a neoplasm: bilateral pleural effusions, Kerley B lines as evident in the right base (arrow), and mediastinal and hilar lymphadenopathy in addition to diffuse parenchymal infiltrate.*

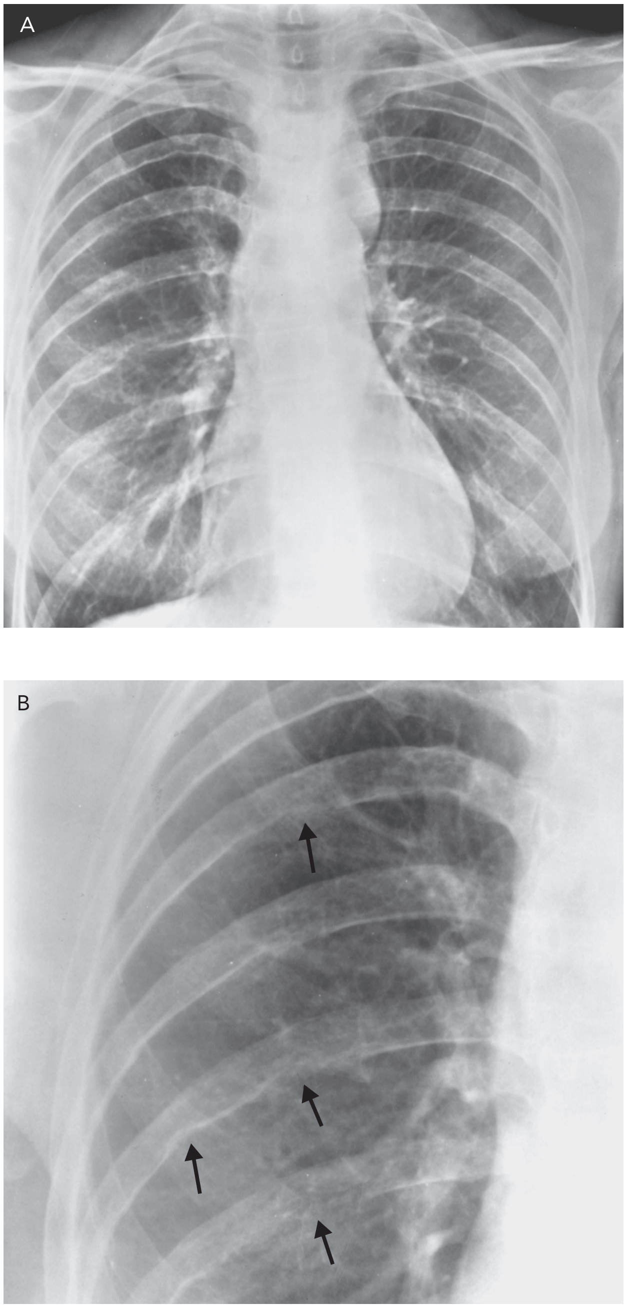

Figure 77.10. Coarctation. A and B, Posteroanterior chest radiographs show coarctation with a tortuous aorta mimicking a mediastinal mass. This occurs in about one-third of patients with coarctation. The arrows in panel B indicate rib notching.

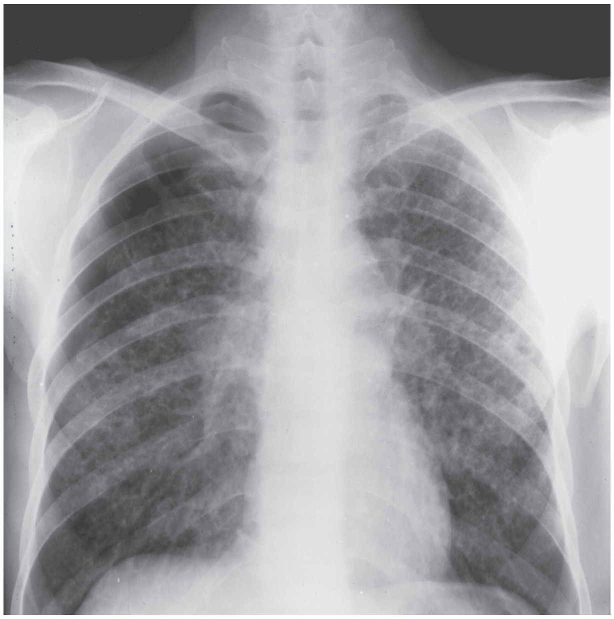

Figure 77.11. Langerhans Cell Histiocytosis (or Eosinophilic Granuloma). Extensive change is predominantly in the upper two-thirds of the lung fields. Eventually 25% of patients have pneumothorax, as seen on this chest radiograph (right side). The honeycombing, also described as microcysts, is characteristic of advanced Langerhans cell histiocytosis.

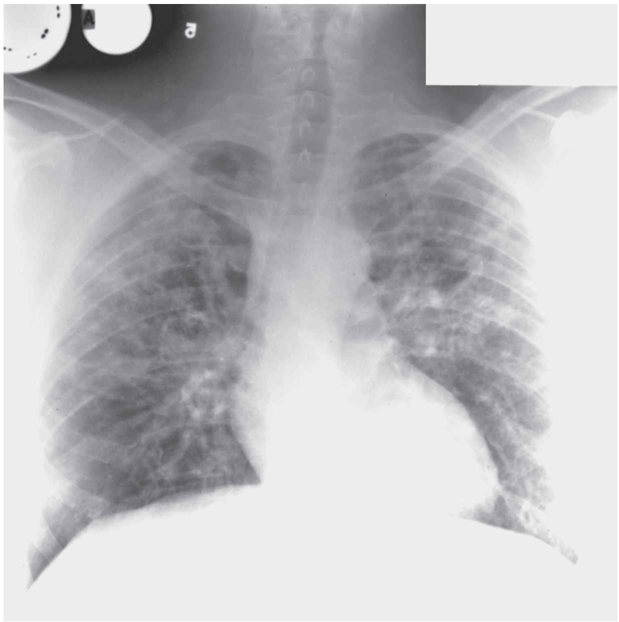

Figure 77.12. Sarcoidosis in a 35-Year-Old Patient. This chest radiograph shows the predominant parenchymal pattern seen in the upper two-thirds of the lungs in many patients with stage II or III sarcoidosis. The pattern can be interstitial, alveolar (which this one is predominantly), or a combination. Some residual adenopathy is probably in the hila and right paratracheal area.

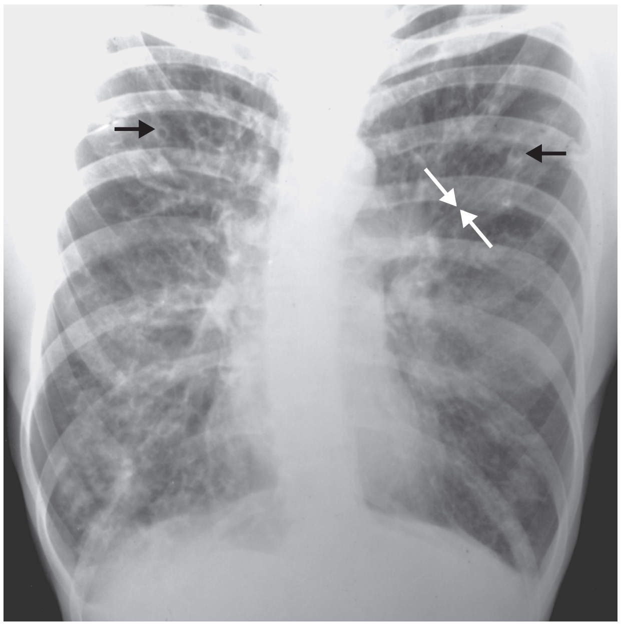

Figure 77.13. *Advanced Cystic Fibrosis. This chest radiograph shows hyperinflation with low-lying hemidiaphragms, bronchiectasis (white arrows pointing to parallel lines), and microabscesses (black arrows), which are small areas of pneumonitis distal to the mucous plug that has been coughed out. Cystic fibrosis almost always begins in the upper lobes.*

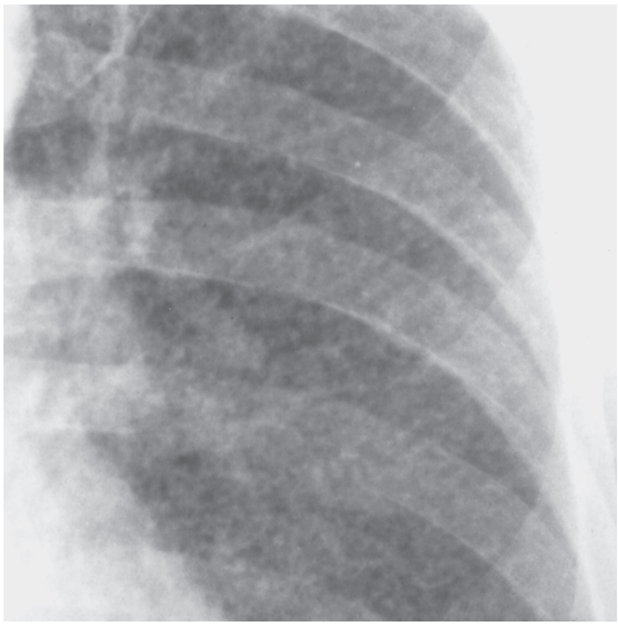

Figure 77.14. *Miliary Tuberculosis. The chest radiograph shows a miliary pattern of relatively discrete micronodules, with little interstitial (linear or reticular) markings. Disseminated fungal disease has a similar appearance, as does bronchoalveolar cell carcinoma; however, the patients do not usually have the systemic manifestations of miliary tuberculosis. Other, less common differential diagnoses include lymphoma, lymphocytic interstitial pneumonitis, and pulmonary edema.* Pneumocystis jiroveci *pneumonia usually has a more interstitial reaction.*

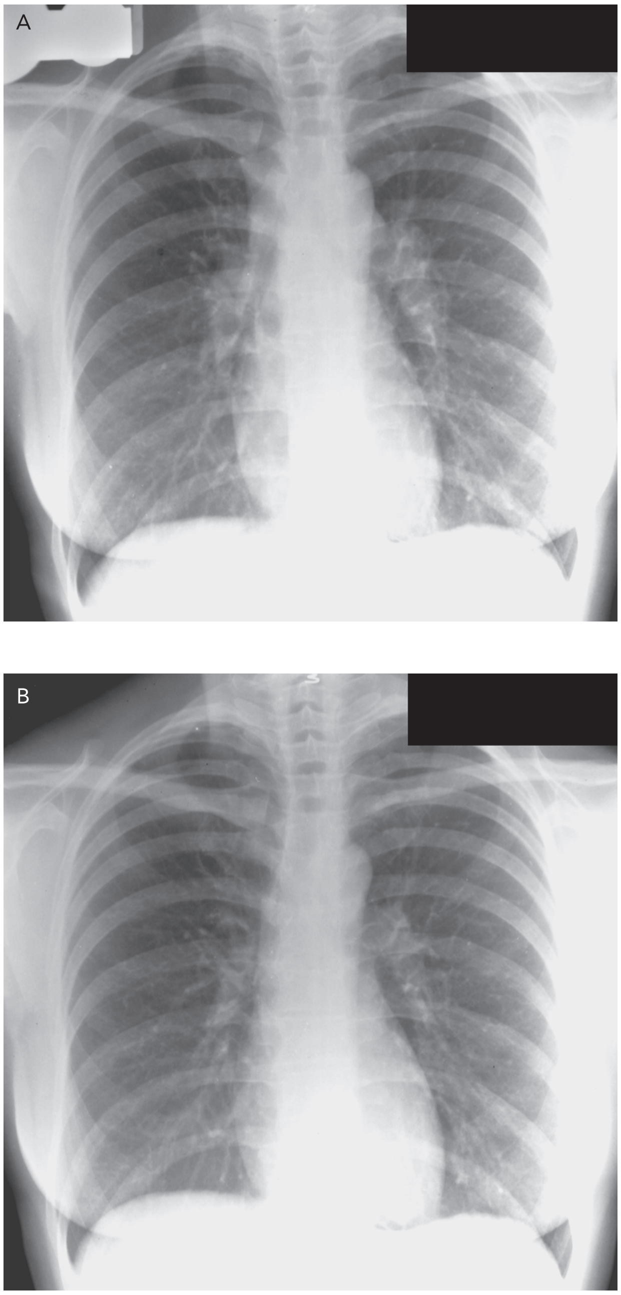

Figure 77.15. *Pulmonary Sarcoidosis. A, Chest radiograph (CXR) of a 30-year-old woman who had stage I pulmonary sarcoidosis with subtle bilateral hilar and mediastinal adenopathy, particularly right paratracheal and left infra-aortic adenopathy. B, CXR 1 year later, after spontaneous regression of sarcoidosis.*

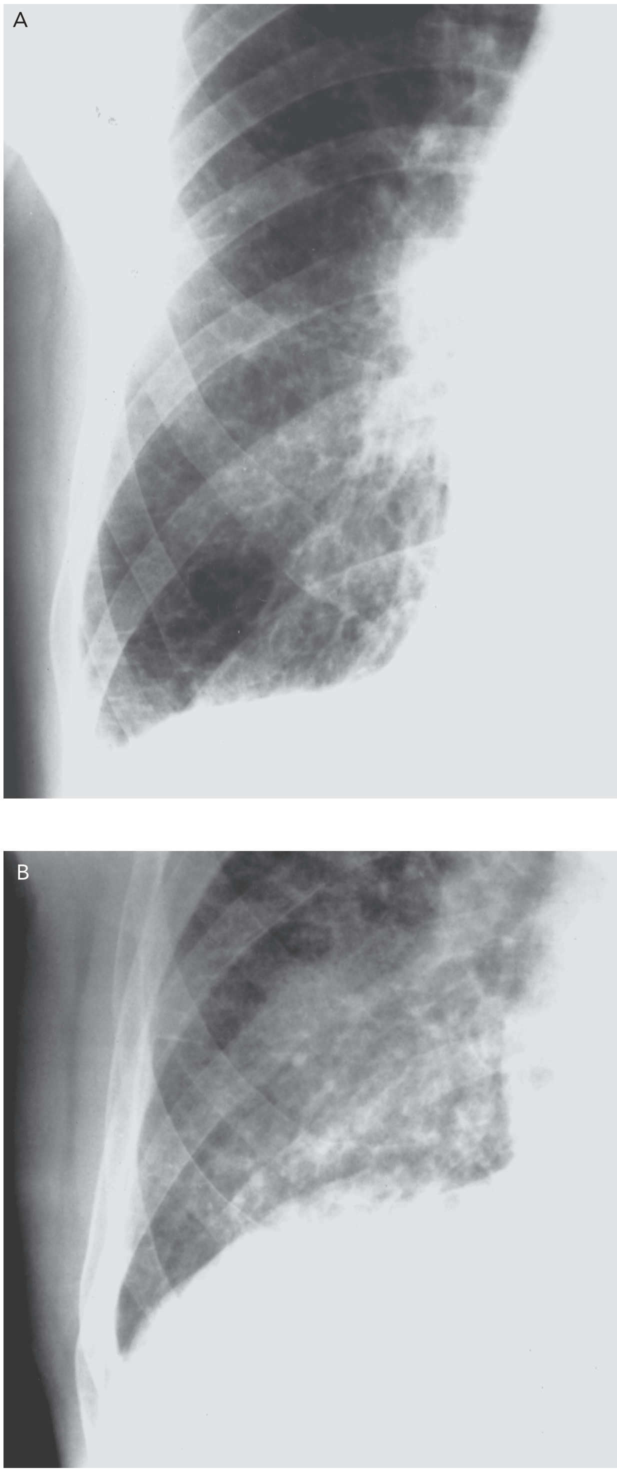

Figure 77.16. *Kerley B Lines. These 2 examples can be helpful in interpreting chest radiographs. A, Kerley B lines are shown in a 75-year-old man with colon cancer. B, The Kerley B lines are from metastatic adenocarcinoma of the colon; they were a tip-off that the parenchymal process in this patient resulted from metastatic carcinoma and not from a primary pulmonary process such as pulmonary fibrosis, which was the working diagnosis.*

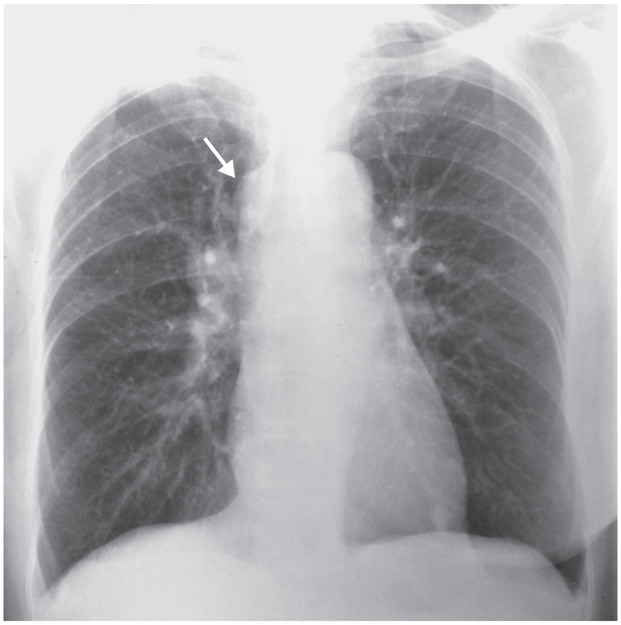

Figure 77.17. *Metastatic Carcinoma of the Breast. This chest radiograph from a 55-year-old woman who had a right mastectomy for breast carcinoma now shows subtle but definite right paratracheal (arrow) and right hilar adenopathy from metastatic carcinoma of the breast.*

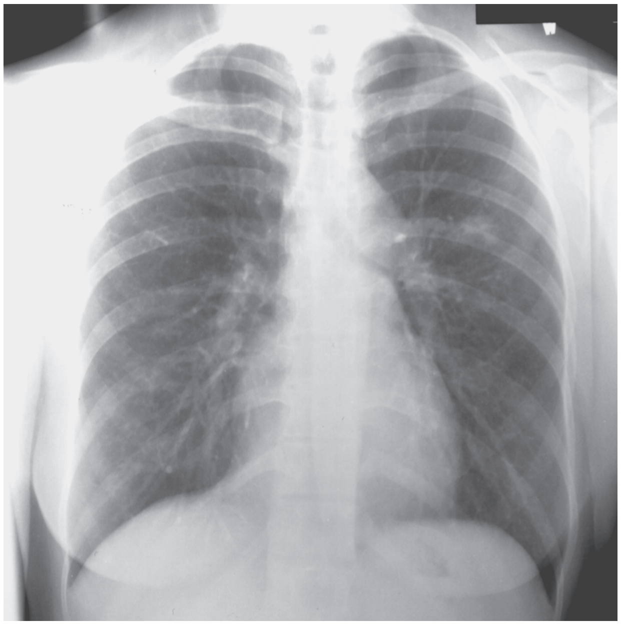

Figure 77.18. *"Solitary Pulmonary Nodule." The nodule in the left midlung field is technically not a solitary pulmonary nodule because of another abnormality in the thorax that might be related: left infra-aortic adenopathy. The differential diagnosis would be bronchogenic carcinoma with hilar nodal metastasis or, as in this patient, acute primary pulmonary histoplasmosis. Had this patient been in an area with coccidioidomycosis, that disease would also be included in the differential diagnosis.*

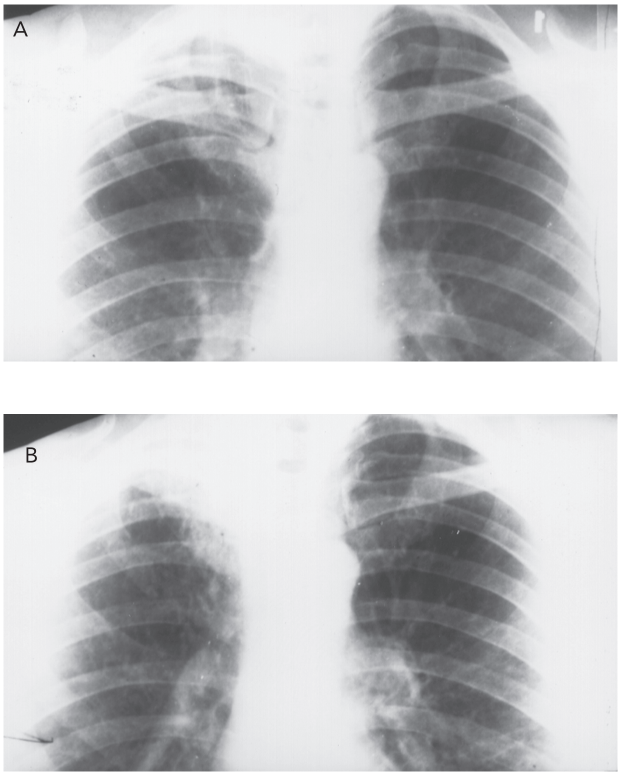

Figure 77.19. *Pancoast Tumor. A, Subtle asymmetry at the apex of the right lung. The patient's symptoms at the initial chest radiography were attributed to a cervical disk. B, The asymmetry was more obvious 3.5 years later when the Pancoast lesion (primary bronchogenic carcinoma) was diagnosed.*

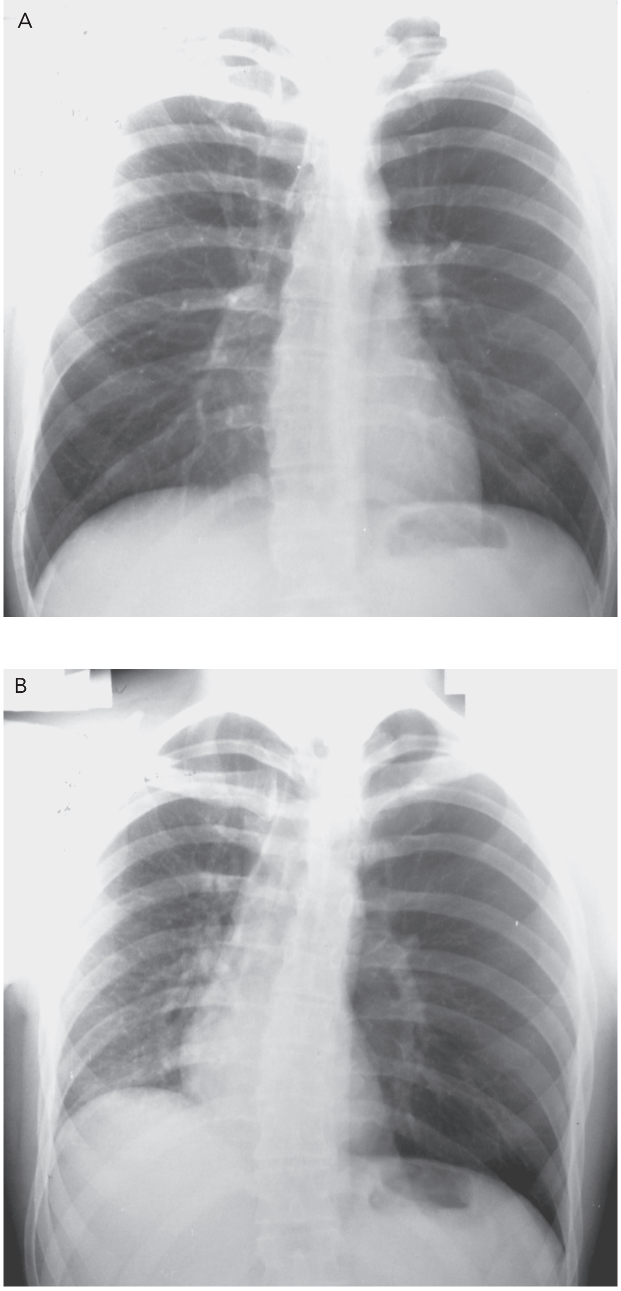

Figure 77.20. *Bronchial Carcinoid. The adage that "not all that wheezes is asthma" should be remembered every time a patient with asthma is encountered and the condition does not seem to improve. A, In this patient, wheezes were predominant over the left hemithorax. B, The forced expiration film showed air trapping in the left lung. Bronchial carcinoid of the left main bronchus was diagnosed at bronchoscopy.*

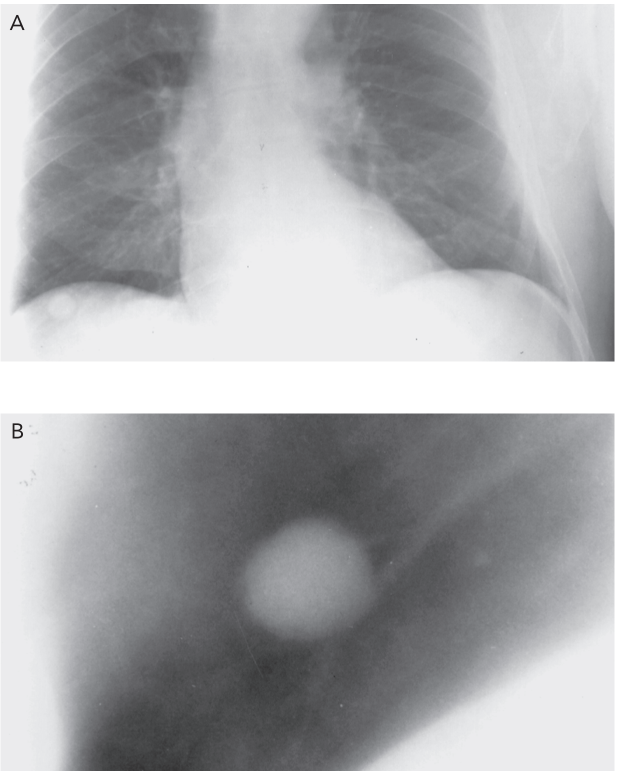

Figure 77.21. Adenocarcinoma. A, A solitary pulmonary nodule is evident below the right hemidiaphragm, where at least 15% of the lung is obscured. B, Computed tomography shows that the nodule has a discrete border but is noncalcified. The nodule was not present 18 months earlier.

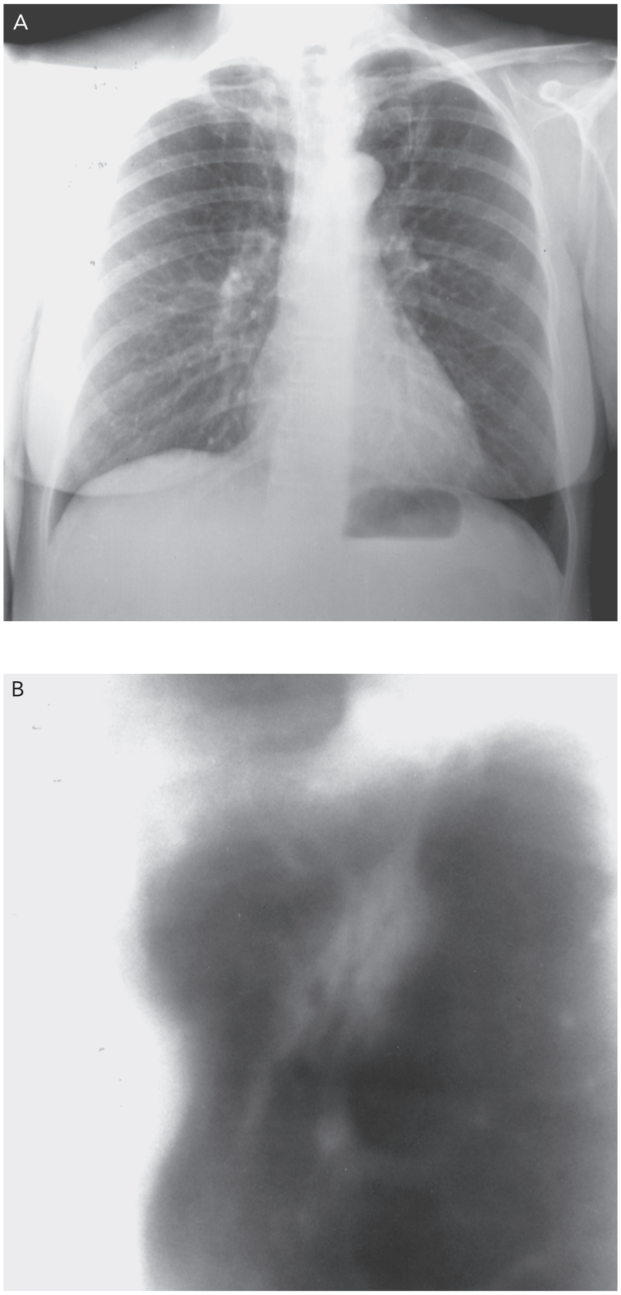

Figure 77.22. Infiltrate. A, Solitary infiltrate in the left upper lobe with air bronchogram, as evident on computed tomography or chest radiography. B, Air bronchogram should be considered a sign of bronchoalveolar cell carcinoma or lymphoma until proved otherwise.

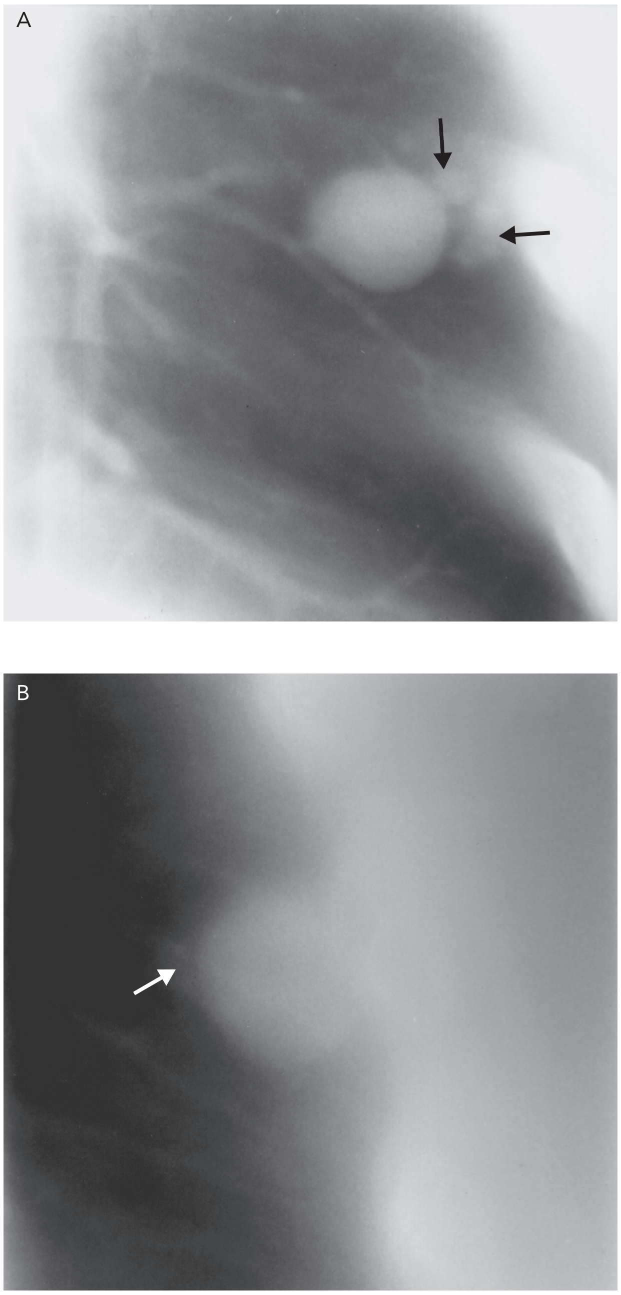

Figure 77.23. *Granuloma. A and B, Computed tomography of solitary pulmonary nodules shows characteristic satellite nodules (arrows).*

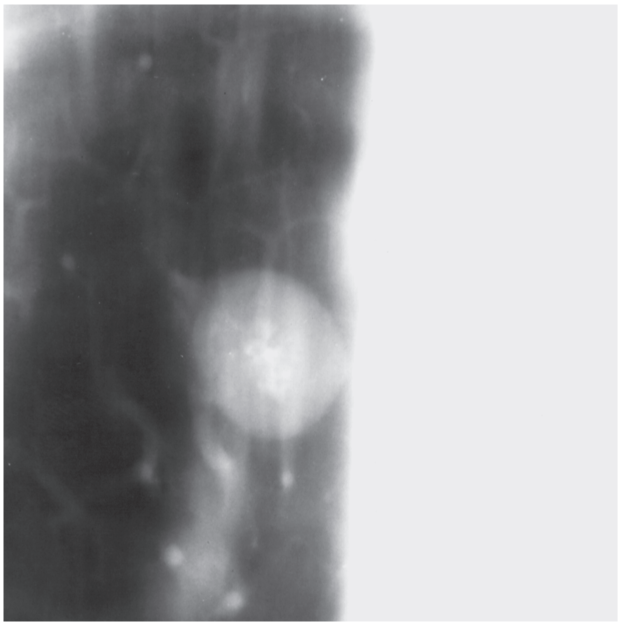

Figure 77.24. *Popcorn Calcification of Hamartoma. This benign process can be seen also with granuloma.*

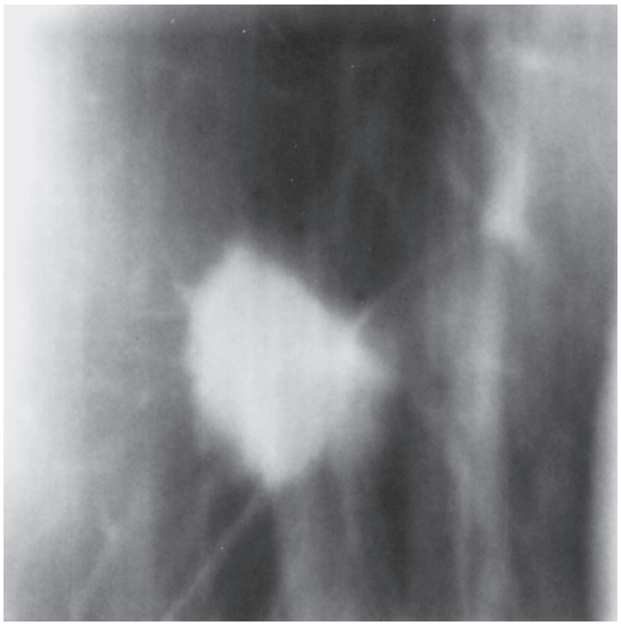

Figure 77.25. *Primary Bronchogenic Carcinoma. Computed tomography of a solitary nodule shows the characteristic spiculation or sunburst effect. Spicules indicate extension of the tumor into the septa. Computed tomography showed a similar appearance.*

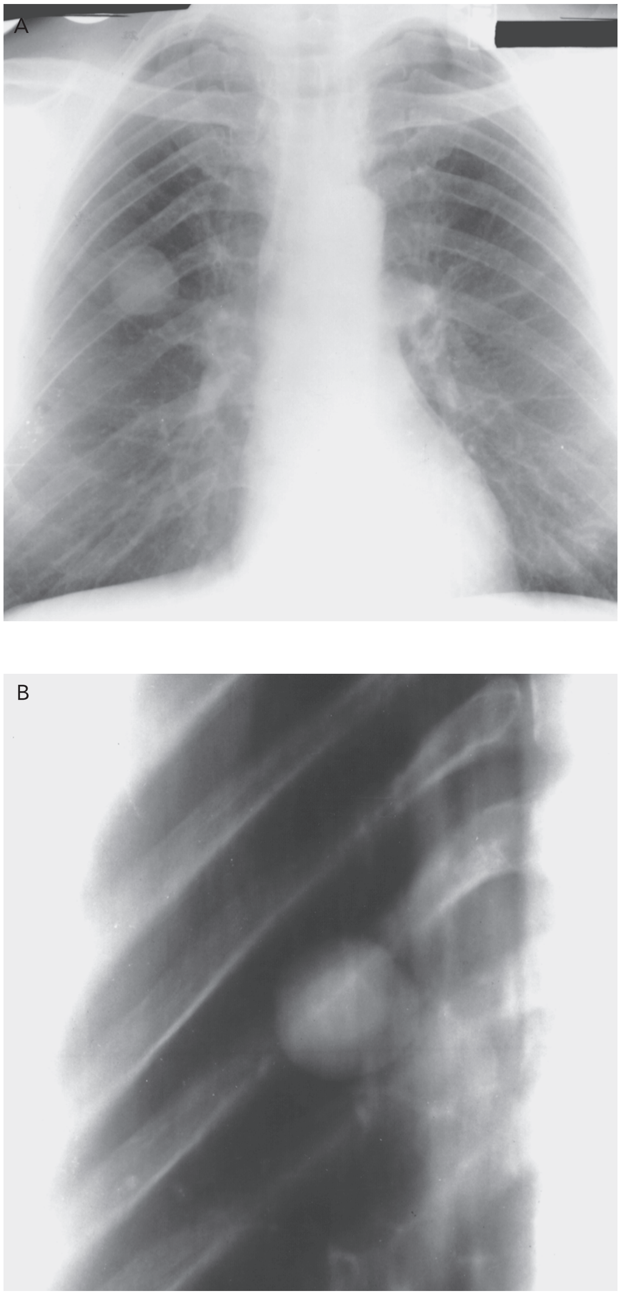

Figure 77.26. *Bull's-Eye Calcification Characteristic of Granuloma in a Solitary Pulmonary Nodule. A and B, These nodules occasionally enlarge but almost never warrant removal.*

Imaging

CT is useful in staging lung cancer and in evaluating the presence of solitary pulmonary nodules, multiple (metastatic) lung nodules, diffuse lung disease, and pleural processes. The use of contrast media helps in diagnosing pulmonary embolism and other pulmonary vascular abnormalities. A high-resolution CT scan is helpful in the evaluation of interstitial lung diseases and can show characteristic features of pulmonary Langerhans cell granulomatosis, lymphangioleiomyomatosis, idiopathic pulmonary fibrosis, and lymphangitic pulmonary metastasis. Magnetic resonance imaging (MRI) is recommended for the initial evaluation of a superior sulcus tumor (ie, a Pancoast tumor), lesions of the brachial plexus, and paraspinal masses that on chest radiography appear consistent with neurogenic tumors. MRI is superior to CT in evaluating chest wall masses and in searching for small occult mediastinal neoplasms (eg, ectopic parathyroid adenoma).

Pulmonary angiography is useful in detecting pulmonary arteriovenous malformations, fistulas, and pulmonary embolisms. Peripheral or tiny pulmonary emboli, however, may not be detected. Bronchial angiography is used for suspected bronchial arterial bleeding in massive hemoptysis. Radionuclide lung scans (also called ventilation-perfusion scans) are useful in the diagnosis of pulmonary embolism, although CT angiography is used increasingly more often. Quantitative radionuclide scans may be useful in assessing unilateral and regional pulmonary perfusion and function before lung resection in surgical candidates who have preoperative comorbidities.

Fluoroscopy is useful in assessing diaphragmatic motion and in diagnosing diaphragmatic paralysis by the sniff test. Paradoxical motion of the diaphragm suggests diaphragmatic paralysis (but it is present in up to 6% of healthy patients). Bilateral diaphragmatic paralysis diminishes the sensitivity of the test.

Pulmonary Function Tests

PFTs are useful in the evaluation of dyspnea (Box 77.3 and Figure 77.27). PFTs can show an obstructive pattern (Figures 77.28-77.31), which suggests diseases such as asthma, chronic obstructive pulmonary disease (COPD), or bronchiectasis. It can also show a restrictive pattern (Figure 77.32) suggestive of interstitial lung disease, chest wall limitation, or neuromuscular weakness. A combination of obstructive and restrictive patterns is also possible (eg, as in patients with combined COPD and pulmonary fibrosis). A **positive bronchodilator response** (ie, an increase of ≥12% *and* a 200-mL increase in either the forced expiratory volume in the first second of expiration [FEV_1] or the forced vital capacity [FVC] after bronchodilator administration) suggests a reversible component to the airway disease, although the absence of a response does not preclude benefit from inhaled bronchodilator medications.

Key Definition

Positive bronchodilator response: *an increase of ≥12% and an increase of ≥200 mL in FEV_1 or FVC after bronchodilator administration.*

Box 77.3 • Interpretation of Pulmonary Function Test Results in the Evaluation of Dyspnea

- Airflow obstruction is indicated by an FEV_1:FVC ratio <70%
  - Severity of airflow obstruction is indicated by the FEV_1, as a percentage of the predicted value
    - Mild obstruction: FEV_1 ≥80% predicted
    - Moderate obstruction: 50%≤ FEV_1 <80% predicted
    - Severe obstruction: 30%≤ FEV_1 <50% predicted
    - Very severe obstruction: FEV_1 <30% predicted
- Airflow restriction is indicated by TLC <80% of the predicted value (a restrictive defect is only suggested by a reduced vital capacity; TLC is needed for confirmation)
  - Severity of restrictive defect is indicated by the TLC as a percentage of the predicted value
    - Mild restriction: 60%≤ TLC <80% predicted
    - Moderate restriction: 50%≤ TLC <60% predicted
    - Severe restriction: TLC <50% predicted
- A positive bronchodilator response requires both an increase of ≥12% *and* an increase of ≥200 mL in the FEV_1 (or FVC) after bronchodilator therapy
- A positive methacholine challenge requires a decrease of ≥20% in the FEV_1 after administration of methacholine

Abbreviations: FEV_1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; TLC, total lung capacity.

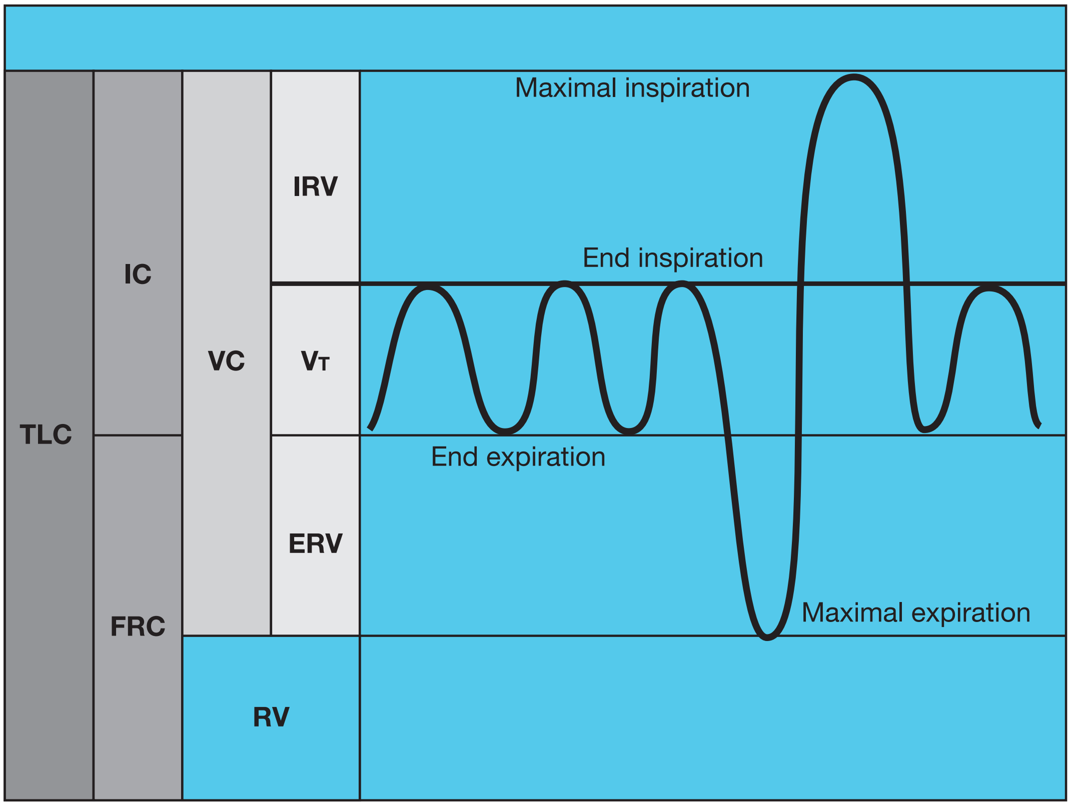

Figure 77.27. Overview of Pulmonary Function Variables. ERV indicates expiratory reserve volume; FRC, functional residual capacity; IC, inspiratory capacity; IRV, inspiratory reserve volume; RV, residual volume; TLC, total lung capacity; VC, vital capacity; V_T, tidal volume.

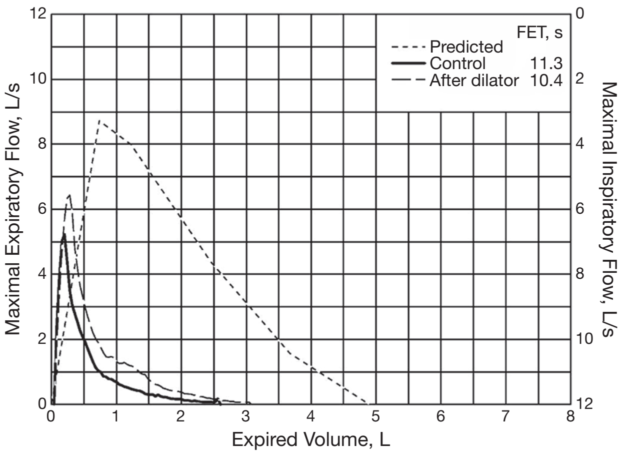

Figure 77.28. *Flow-Volume Curve From a Patient With Obstruction. FET indicates forced expiratory time.*

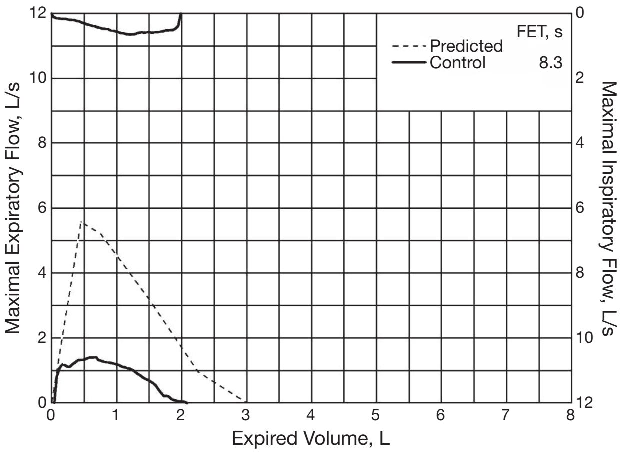

Figure 77.29. *Flow-Volume Curve From a Patient With Central Airway Obstruction. FET indicates forced expiratory time.*

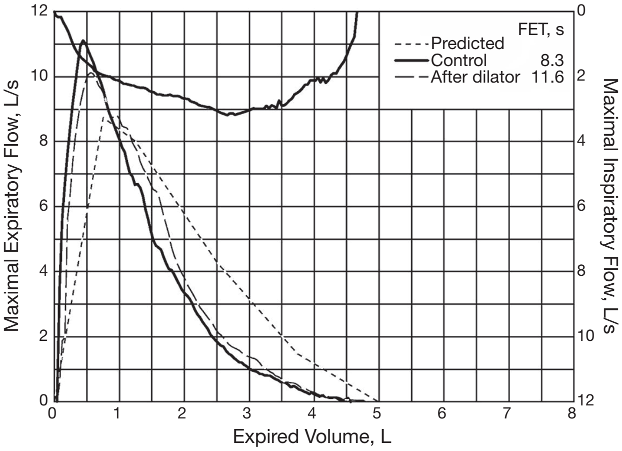

Figure 77.30. *Flow-Volume Curve From a Patient With Variable Extrathoracic Obstruction. FET indicates forced expiratory time.*

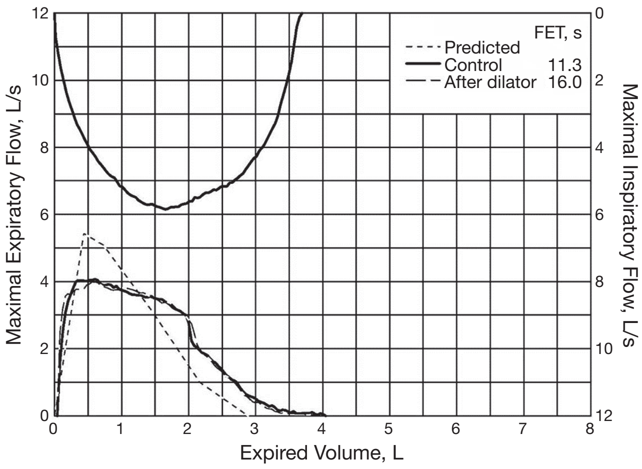

Figure 77.31. *Flow-Volume Curve From a Patient With Variable Intrathoracic Obstruction. FET indicates forced expiratory time.*

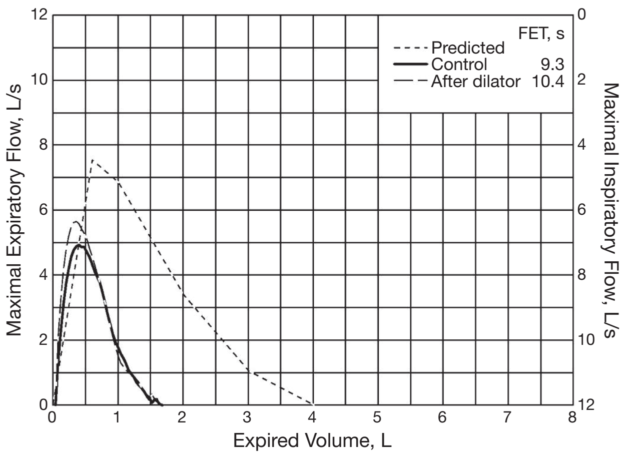

Figure 77.32. *Flow-Volume Curve From a Patient With Restriction. FET indicates forced expiratory time.*

Provocation inhalational challenge with a bronchospastic agent (eg, methacholine or exercise) is useful when the diagnosis of asthma or hyperreactive airway disease is uncertain. A response is considered to be positive if the FEV_1 decreases at least 20% after methacholine inhalation, although up to 10% of healthy patients show a positive response to an inhalational challenge. A negative response is helpful in ruling out hyperreactive airway disease. A false-positive response can result from airway hyperreactivity due to recent infection or inflammation.

A simplified approach to interpreting PFT results is shown in Box 77.4.

Hypothetical PFT Results

Hypothetical PFT results are shown in Table 77.2 for 9 patients. The results should be interpreted before the following explanations are read.

Box 77.4 • Simplified Step-by-step Approach to Interpreting PFT Results

1. Volumes and flows are evaluated separately.
2. The flow-volume curve may suggest an obstructive pattern ("scooped out" appearance) or a restrictive pattern (high peak with narrow curve).
3. An FEV_1:FVC ratio <70% suggests airflow obstruction. FEV_1 is used to classify the severity of airflow obstruction (Box 77.3).
4. If the FEV_1:FVC ratio is ≥70% but the FEV_1 is reduced, the TLC should be evaluated because a reduced TLC suggests a restrictive defect (Box 77.3).
5. TLC, FRC, and RV indicate volumes. TLC = VC + RV. Increases in TLC and RV suggest hyperinflation (asthma or COPD). If TLC and VC are decreased, restrictive lung disease (fibrosis) or loss of lung volume (surgery, diaphragmatic paralysis, or skeletal problems) should be considered.
6. VC measured during a slow (not forced) expiration is not affected by airway collapse in COPD. In obstructive airways disease, the FVC may be decreased with forced expiration because of airway collapse. In healthy patients, VC = FVC.
7. The FEV_1 and FEF of the midexpiratory phase ($FEF_{25\%-75\%}$) indicate flow rates. Flow rates are diminished in COPD, but decreases can be smaller if lung volumes are low.
8. The MVV test requires rapid inspiratory and expiratory maneuvers and, thus, tests airflow through major airways and muscle strength. Disproportionately reduced MVV ($MVV = FEV_1 \times 35$) may be from poor effort, variable extrathoracic obstruction, or respiratory muscle weakness. Respiratory muscle weakness can be assessed by maximum inspiratory pressure (PImax) and maximum expiratory pressure (PEmax). Clinical features should be correlated with the results of PFTs.
9. DLCO is dependent on the thickness of the alveolar-capillary membrane (T), the area of the alveolar-capillary membrane (A), and the pressure difference between alveolar gas and venous blood (ΔP_{CO}). Thus, DLCO is represented by the following:

$$D_{LCO} = \frac{A \times \Delta P_{CO}}{T},$$

where ΔP_{CO} is the change in the partial pressure of carbon monoxide.

   Causes of low DLCO
      - Anatomical emphysema (decreased A)
      - Anemia (effectively decreased A) (a decrease in hemoglobin by 1 g/dL diminishes DLCO by 7%)
      - Restrictive lung diseases (decreased A or decreased T in pulmonary fibrosis or other interstitial lung diseases)
      - Pulmonary hypertension (effectively decreased T)
      - Recurrent pulmonary emboli (effectively decreased A)

   Causes of increased DLCO
      - Supine posture (increased A due to increased blood volume in upper lobes)
      - Exercise (increased A due to increased blood volume)
      - Polycythemia (increased A)
      - Obesity (increased A due to increased blood volume)
      - Left-to-right shunt (increased A)
      - Asthma (in some patients)

   Causes of isolated low DLCO (with normal PFT results)
      - Pulmonary hypertension
      - Multiple pulmonary emboli
      - Combined diseases (eg, pulmonary fibrosis with COPD)
      - Anemia

10. Flow-volume curves are helpful to distinguish between intrathoracic and extrathoracic major airway obstructions. Flattening of the expiratory flow curve with a normal inspiratory flow curve suggests intrathoracic airway obstruction. Flattening of the inspiratory flow curve alone suggests extrathoracic airway obstruction. Flattening of both flow curves suggests fixed airway obstruction, and the location cannot be determined.

Abbreviations: COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity of lung for carbon monoxide; FEF, forced expiratory flow; FEV_1, forced expiratory volume in the first second of expiration; FRC, functional residual capacity; FVC, forced vital capacity; MVV, maximal voluntary ventilation; PFT, pulmonary function test; RV, residual volume; TLC, total lung capacity; VC, vital capacity.

Patient 1

The patient has typical features of emphysema. The FEV_1:FVC ratio indicates obstruction. The FEV_1 indicates that the obstruction is severe. The total lung capacity (TLC) indicates hyperinflation. The reduced diffusing capacity of lung for carbon monoxide (DLCO) suggests emphysema. The clinical diagnosis is severe COPD with anatomical emphysema.

Patient 2

The PFT results suggest emphysema. In a young nonsmoker, other causes of emphysema must be considered. The clinical diagnosis is severe emphysema caused by familial deficiency of α_1-antitrypsin.

Patient 3

Flow rates and lung volumes are decreased only slightly but are within normal limits. The maximal voluntary ventilation (MVV) is severely decreased. In this patient, maximum inspiratory pressure (PImax) and maximum expiratory pressure (PEmax) were severely decreased, suggesting muscle weakness. The clinical diagnosis is severe thyrotoxicosis with proximal

Table 77.2 • Hypothetical Results of Pulmonary Function Tests for 9 Patients

	Patient								
Feature	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Age, y	73	43	53	43	20	58	40	28	44
Sex	M	M	F	M	M	F	M	F	M
Weight, kg	52	53	50	63	80	59	75	52	148
Tobacco, PY	63	NS	NS	NS	NS	NS	NS	NS	NS
Total lung capacity, %[a]	140	128	84	118	100	56	68	108	90
Vital capacity, %[a]	52	75	86	78	95	62	58	106	86
Residual volume, %[a]	160	140	90	110	90	65	80	98	90
FEV$_1$, %[a]	35	38	82	48	90	85	42	112	96
FEV$_1$:FVC ratio, %	40	34	80	40	85	88	50	85	78
FEF$_{25\%-75\%}$, %[a]	18	14	80	35	88	82	24	102	88
Maximum voluntary ventilation, %[a]	62	48	40	60	120	108	62	88	90
DLCO (reference value), mL/min/mm Hg	9(22)	10(28)	20(20)	28(28)	32(34)	8(26)	8(28)	6(32)	40(28)

Abbreviations: DLCO, diffusing capacity of lung for carbon monoxide; FEF$_{25\%-75\%}$, forced expiratory flow of the midexpiratory phase; FEV$_1$, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; NS, nonsmoker; PY, pack-years of smoking.

[a] Percentage of the predicted value. Values from 80% to 120% are considered the reference range.

muscle weakness (ie, thyrotoxic myopathy). This pattern of PFT results can also occur when patients have neuromuscular diseases such as amyotrophic lateral sclerosis and myasthenia gravis.

Patient 4

The FEV$_1$:FVC ratio and the FEV$_1$ indicate a moderately severe airflow obstruction. The normal TLC and residual volume suggest an absence of air trapping. The normal DLCO excludes anatomical emphysema or other parenchymal problems. Bronchodilator testing elicited improvement in lung volumes and flow rates. The clinical diagnosis is typical asthma.

Patient 5

This patient has normal lung volumes and flow rates (80%-120% of the predicted normal). A former athlete, he recently noted cough and chest tightness after exertion. Previous PFT results were unavailable. The following are important points: 1) In a young, otherwise healthy patient, the lung volumes and flow rates are usually greater than normal and even higher in an athlete. 2) This patient may have had very high volumes and flow rates in the past, but without previous PFT results, no comparison can be made (if earlier PFT results were available, the new results might show a severe decrease in pulmonary function). 3) The history suggests the possibility of exercise-induced asthma; spirometry after an exercise test showed a 28% reduction in flow rates 5 to 10 minutes after exercise ended. 4) The relatively high DLCO is a phenomenon in patients with asthma. The clinical diagnosis is exercise-induced asthma.

Patient 6

This patient has a moderately severe decrease in lung volumes and normal flow rates. The MVV is normal, but the DLCO is severely diminished. These results suggest severe restrictive lung disease. The slightly diminished flow rates are the result of decreased lung volumes. The clinical diagnosis is biopsy-proven idiopathic pulmonary fibrosis. Patients who have had lung resection also have low lung volumes and decreased DLCO.

Patient 7

The reduction in the FEV$_1$:FVC ratio suggests the presence of obstructive dysfunction. The decreased TLC suggests additional restrictive lung disease. The MVV is also reduced, and the DLCO is severely decreased. This patient has COPD and severe restrictive lung disease. A very low DLCO suggests parenchymal disease. Chest radiography showed bilaterally diffuse nodular interstitial changes, especially in the upper two-thirds of the lungs. Biopsy specimens of the bronchial mucosa and lung showed extensive endobronchial sarcoidosis. The clinical diagnosis is severe restrictive lung disease from parenchymal sarcoidosis and obstructive dysfunction caused by endobronchial sarcoidosis.

Patient 8

This patient has normal lung volumes and flow rates. The MVV is slightly decreased but within normal limits. The Dlco is very low. The Pa_{O_2} is 56 mm Hg. The clinical diagnosis is primary pulmonary hypertension.

Patient 9

This extremely obese patient has normal lung volumes and flow rates. The Dlco is abnormally high. Abnormally high Dlco is reported to be a result of increased vital capacity. The clinical diagnosis is obesity-related pulmonary dysfunction.

KEY FACTS

✓ Provocation inhalational challenge with bronchospastic agent (eg, methacholine)—

- useful when diagnosis of asthma or hyperreactive airway disease is uncertain
- positive response: decrease of ≥20% in FEV_1 after inhalation of methacholine

✓ FEV_1:FVC ratio—

- <70% suggests airflow obstruction (FEV_1 is used to classify severity)
- ≥70% with a decreased FEV_1 should prompt evaluation of TLC (a decreased TLC suggests a restrictive defect)

✓ Causes of disproportionately reduced MVV—poor effort, variable extrathoracic obstruction, or respiratory muscle weakness

✓ Causes of low Dlco—

- anatomical emphysema (smaller area of the alveolar-capillary membrane)
- anemia (effectively smaller area of the alveolar-capillary membrane); Dlco decreases by 7% for each 1-g/dL decrease in hemoglobin
- restrictive lung diseases (in pulmonary fibrosis or other interstitial lung diseases, alveolar-capillary membrane is smaller in area or thinner)
- pulmonary hypertension (effectively thinner alveolar-capillary membrane)

✓ Flow curve patterns that help distinguish between intrathoracic and extrathoracic airway obstruction—

- flattened expiratory flow curve with normal inspiratory flow curve: intrathoracic airway obstruction
- flattened inspiratory flow curve alone: extrathoracic airway obstruction
- flattened expiratory and flattened inspiratory flow curves: fixed airway obstruction (undetermined location)

Exercise Testing

Indications for cardiopulmonary exercise testing include unexplained dyspnea or effort intolerance, disability evaluation, quantification of the severity of pulmonary dysfunction, differentiation between cardiac and pulmonary causes of disability, evaluation of progression of a disease process, estimation of operative risks before cardiopulmonary surgery (eg, lung resection, heart-lung transplant, or lung transplant), rehabilitation, and evaluation of the need for supplemental oxygen during exercise.

Invasive Testing

Bronchoscopy can be used for diagnostic and therapeutic purposes. It can be helpful in the evaluation of persistent cough, hemoptysis, pulmonary nodules, atelectasis, diffuse lung disease, lung infections, suspected cancer, and staging of lung cancer. Therapeutic indications include atelectasis, retained secretions, tracheobronchial foreign bodies, airway stenosis, and obstructive lesions. Bronchoalveolar lavage is helpful in diagnosing lung infections. Lung biopsy can be done with bronchoscopy, thoracoscopy, or thoracotomy.

78

Pulmonary Vascular Disease[a]

RODRIGO CARTIN-CEBA, MD, MSc

Pulmonary Hypertension

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure (mPAP) of 25 mm Hg or higher at rest, as measured during right heart catheterization (RHC). The many causes of PH are classified into 5 groups (Box 78.1).

> Key Definition
>
> **Pulmonary hypertension:** *mPAP ≥25 mm Hg at rest, as measured during RHC.*

Group 1, **pulmonary arterial hypertension** (PAH), is characterized by precapillary PH, normal pulmonary capillary wedge pressure (<15 mm Hg), and increased vascular resistance (>3 Wood units), which leads to right-sided heart failure and death. *Idiopathic PAH* describes a subcategory of PAH. PAH is treated with pulmonary artery–vasodilator therapy. Pulmonary artery–vasodilator therapy is also used in some patients with group 4 PH (chronic thromboembolic pulmonary hypertension). Treatment of PH from other causes (groups 2, 3, and 5) is predominantly aimed at the underlying cause, and patients with PH due to those causes usually do not benefit from pulmonary artery–vasodilator therapy.

> Key Definition
>
> **Pulmonary arterial hypertension:** *precapillary PH, normal pulmonary capillary wedge pressure (<15 mm Hg), and increased vascular resistance (which leads to right-sided heart failure and death).*

The clinical presentation of patients with PH is nonspecific: progressive dyspnea, chest pain, lower extremity edema, and fatigue. Blood testing, which may be helpful for identifying a cause of PH, includes connective tissue serologies, human immunodeficiency virus (HIV) testing, N-terminal pro-brain natriuretic peptide (NT-proBNP), thyroid and liver testing, and a complete blood cell count. Full pulmonary function testing, ventilation-perfusion scanning to assess for chronic thromboembolic disease, and sleep studies are essential in the evaluation.

Typically, a diagnosis of PH is suggested by an increased right ventricular systolic pressure on transthoracic Doppler echocardiography and is confirmed with RHC. Hemodynamic measurements during RHC are important for excluding PH due to left-sided heart failure (with reduced or preserved ejection fraction) and contributions from high cardiac output (eg, liver disease, thyroid disease, or anemia). Acute vasoreactivity testing is mandatory for patients with idiopathic PAH or heritable PAH

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[a] Portions previously published in Cartin-Ceba R, Swanson KL, Krowka MJ. Pulmonary arteriovenous malformations. Chest. 2013 Sep;144(3):1033-44; used with permission.

Box 78.1 • Updated Clinical Classification of Pulmonary Hypertension[a]

1. Pulmonary arterial hypertension (PAH)
   1.1. Idiopathic PAH
   1.2. Heritable PAH
      1.2.1. BMPR2
      1.2.2. ALK1, ENG, **SMAD9**, **CAV1**, **KCNK3**
      1.2.3. Unknown
   1.3. Drug and toxin induced
   1.4. Associated with
      1.4.1. Connective tissue disease
      1.4.2. HIV infection
      1.4.3. Portal hypertension
      1.4.4. Congenital heart diseases
      1.4.5. Schistosomiasis

1′. Pulmonary venoocclusive disease or pulmonary capillary hemangiomatosis (or both)

1″. Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension due to left heart disease
   2.1. Left ventricular systolic dysfunction
   2.2. Left ventricular diastolic dysfunction
   2.3. Valvular disease
   2.4. **Congenital or acquired left heart inflow tract or outflow tract obstruction and congenital cardiomyopathies**
3. Pulmonary hypertension due to lung diseases or hypoxia (or both)
   3.1. Chronic obstructive pulmonary disease
   3.2. Interstitial lung disease
   3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
   3.4. Sleep-disordered breathing
   3.5. Alveolar hypoventilation disorders
   3.6. Chronic exposure to high altitude
   3.7. Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
   5.1. Hematologic disorders: **chronic hemolytic anemia,** myeloproliferative disorders, splenectomy
   5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, **segmental PH**

Abbreviations: ALK1, activin receptor-like kinase type 1; BMPR2, bone morphogenic protein receptor type 2; CAV1, caveolin 1; ENG, endoglin; KCNK3, potassium channel, 2-pore domain subfamily K, member 3; SMAD9, SMAD family member 9.

[a] From the 5th World Symposium on Pulmonary Hypertension held in Nice, France, in 2013. The main modifications to the previous Dana Point (2008) classification are in boldface type.

From Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013 Dec 24;62(25 Suppl):D34-41. Erratum in: J Am Coll Cardiol. 2014 Feb 25;63(7):746; used with permission.

to identify patients who may respond favorably to treatment with calcium channel blockers.

World Health Organization (WHO) functional class is a powerful predictor of survival. Median survival of patients in WHO functional class I or II is 6 years; for patients in WHO functional class IV, median survival is 6 months. Decreased exercise capacity (6-minute walk distance), advanced functional class, syncope, presence of pericardial effusion, and signs of right ventricular failure carry a poor prognosis.

To date, no cure exists. However, several treatment options that target the pulmonary artery have been shown to improve quality of life and possibly survival. Several pulmonary artery–targeted drugs acting through 5 different mechanisms are currently approved for the treatment of PAH (group 1) (Table 78.1). Combination therapy has become the standard of care in PAH, although the long-term safety and efficacy data are not well defined. A stepwise approach appears beneficial.

Table 78.1 • Approved Pulmonary Artery–Targeted Drugs for the Treatment of Pulmonary Arterial Hypertension

Drug Group	Approved Drugs	Administration Route
Prostacyclin analogues	Epoprostenol	Intravenous
	Treprostinil	Intravenous Subcutaneous Inhaled Oral
	Iloprost	Inhaled
Nonprostanoid prostacyclin receptor agonist	Selexipag	Oral
Phosphodiesterase type 5 inhibitors	Sildenafil Tadalafil	Oral Oral
Endothelin receptor antagonist	Bosentan Ambrisentan Macitentan	Oral Oral Oral
Guanylate cyclase stimulator	Riociguat	Oral

Drug-drug interactions are common. Oxygen, diuretics, digoxin, and anticoagulation may be useful in the treatment of PAH. Recommendations include participating in supervised exercise training, avoiding pregnancy, and receiving both influenza and pneumococcal vaccinations. Pulmonary artery–targeted therapy in PAH has reduced referral for lung transplant, but transplant is an important option for patients who do not have a response to medical therapy.

Untreated PH induces hypertrophy and dilatation of the right ventricle, which results in impaired function that leads to signs and symptoms of right ventricular failure, including increased jugular venous pressure, lower extremity edema, hepatomegaly and ascites. The term *cor pulmonale* is used only for right ventricular failure secondary to PH due to chronic lung disease or hypoxemia (group 3).

Pulmonary Vasculitides and Alveolar Hemorrhage Syndromes

The pulmonary vasculitides are a heterogeneous group of autoimmune disorders characterized by inflammation and necrosis of the small pulmonary vessels. The most common vasculitides affecting the lungs are the antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides, including granulomatosis with polyangiitis (formerly known as Wegener granulomatosis), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome). These conditions are reviewed in Chapter 84, “Vasculitis.”

Hemorrhage into the alveolar spaces is called diffuse alveolar hemorrhage (DAH) syndrome. DAH is often characterized by the presence of cough, dyspnea, fever, and chest pain with or without hemoptysis. Bilateral alveolar infiltrates are often observed on chest imaging. Diagnosis is established with bronchoalveolar lavage (BAL) that shows progressively bloody return or an elevated number of hemosiderin-laden macrophages (>20%) or both. DAH is often associated with ANCA-associated vasculitides, connective tissue diseases such as systemic lupus erythematosus, and anti–glomerular basement membrane (GBM) disease; these entities can occur as renal-pulmonary syndromes with both DAH and glomerulonephritis. Immunologic-mediated DAH is treated by administering high-dose intravenous methylprednisolone and addressing the underlying cause; plasma exchange may be indicated in certain cases (ie, Goodpasture syndrome).

Anti-GBM Disease (Goodpasture Syndrome)

Anti-GBM disease is a classic example of a cytotoxic (type II) disease in which autoantibodies target the GBM and the alveolar basement membrane. Younger patients with anti-GBM disease most often present with Goodpasture syndrome and recurrent hemoptysis, dyspnea, anemia, hematuria, and renal failure (pulmonary hemorrhage and rapidly progressive glomerulonephritis). The typical patient is a young man in his 20s (male to female ratio, 7:1) with pulmonary symptoms preceding renal manifestations. Among older patients with anti-GBM disease, women are affected more than men, and patients usually present with glomerulonephritis alone.

Kidney biopsy shows diffuse necrotizing crescentic glomerulonephritis, and immunofluorescence staining shows linear deposition of immunoglobulin (Ig)G and complement along basement membranes. Anti-GBM antibody is positive in more than 90% of patients.

Plasmapheresis is the treatment of choice to remove the circulating autoantibodies, and cyclophosphamide and systemic corticosteroids are used to stop production of new autoantibodies. Complete recovery is expected in most patients; relapse occurs in up to 7% of patients.

Pulmonary Arteriovenous Malformation

Pulmonary arteriovenous malformations (PAVMs) are abnormal vascular structures that most often connect a pulmonary artery to a pulmonary vein, resulting in an intrapulmonary right-to-left shunt (Figure 78.1). As a consequence, patients present with hypoxemia and paradoxical embolization complications, including transient ischemic attack (TIA), stroke, and brain abscess. PAVMs lack structural integrity and can rupture, leading to hemorrhagic complications, including hemoptysis and hemothorax. Most PAVMs are hereditary and occur with hereditary hemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber syndrome, an autosomal dominant vascular disorder.

Diagnostic criteria for HHT include telangiectasias (fingers, lips, and tongue), epistaxis (spontaneous and recurrent), visceral arteriovenous malformation (brain, lung, liver, and gastrointestinal tract), and family history. Diagnostic testing involves identifying an intrapulmonary shunt—the most sensitive test is transthoracic contrast echocardiography. Computed tomography of the chest is useful for characterizing PAVM in patients who have intrapulmonary shunting. Transcatheter embolotherapy is the treatment of choice for PAVM. Lifelong follow-up is important because recanalization and collateralization may occur after embolization therapy. Surgical resection is rarely necessary, and it is reserved for patients who are not candidates for embolization. Antibiotic prophylaxis for procedures with a risk of bacteremia (eg, dental procedures) is recommended for all patients with PAVM because of the risk of cerebral abscess.

Hepatopulmonary Syndrome

Hepatopulmonary syndrome (HPS) is a complication of portal hypertension. The diagnostic triad includes evidence of portal hypertension, intrapulmonary vascular dilatations, and hypoxemia. Hypoxemia is identified by a

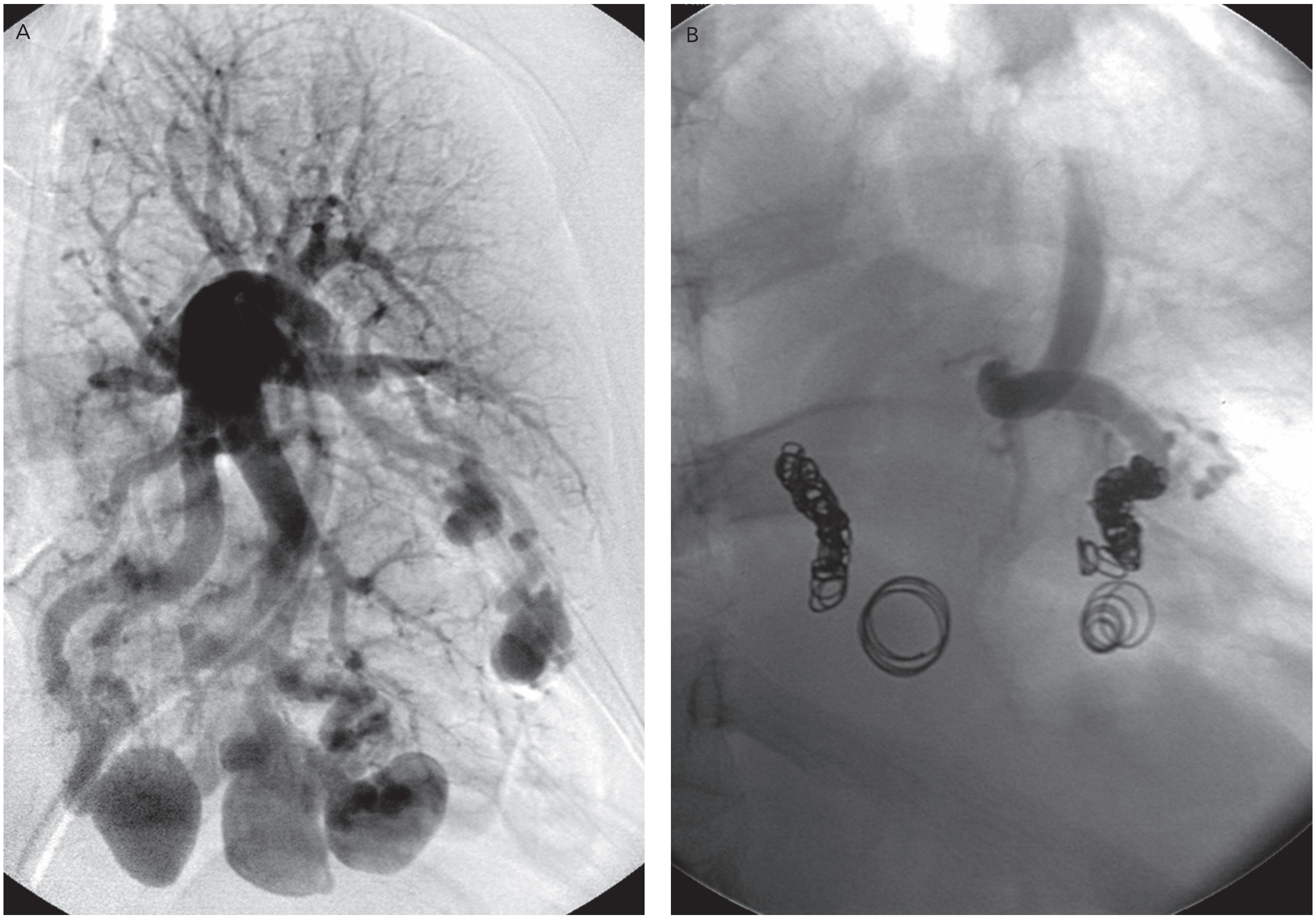

Figure 78.1. *Pulmonary Arteriovenous Malformations.*
A, Pulmonary angiography documents the presence of multiple, large pulmonary arteriovenous malformations. B, After coil embolization, the pulmonary arteriovenous malformations show a complete lack of flow.

low $Pa\text{O}_2$ on arterial blood gas analysis (<80 mm Hg with room air) or an increased alveolar-arterial gradient in the $P\text{O}_2$. Intrapulmonary vascular dilatations are identified on contrast-enhanced echocardiography (bubble study), and the degree of shunting can be determined from a perfusion lung scan with technetium 99m–labelled macroaggregated albumin. Classic symptoms of HPS are platypnea-orthodeoxia (dyspnea upon changing to an upright position); clubbing and cyanosis may be seen on examination. The only effective treatment is liver transplant, which resolves hypoxemia and improves survival.

Pulmonary Artery Aneurysm

Pulmonary artery aneurysms are usually asymptomatic and are discovered on routine chest imaging. Many patients do not require treatment other than serial observation. Surgical indications include recurrent hemoptysis, continued growth, or refractory hypoxemia because of right-to-left shunting through the aneurysm.

Pulmonary Capillary Hemangiomatosis

Pulmonary capillary hemangiomatosis is a severe, idiopathic proliferation of pulmonary capillaries that is usually accompanied by PH. Symptoms include dyspnea, hemoptysis, and edema. Computed tomography shows a diffuse reticulonodular pattern with enlarged central pulmonary arteries. The diagnosis requires lung biopsy, which is usually not performed owing to excessive risk. There is no effective treatment. Without transplant, median survival is 3 years.

Pulmonary Vascular Tumors

Pulmonary vascular tumors are rare and are usually metastatic at diagnosis. They may arise from the aorta, inferior vena cava, pulmonary arteries, or veins. Sarcomas and leiomyosarcomas are the most common tumors and may mimic pulmonary embolism. Breast, lung, prostate, pancreas, liver, and stomach cancers may metastasize to the pulmonary vasculature.

KEY FACTS

✓ Tests to identify a cause of PH—
  - connective tissue serologies
  - HIV testing
  - NT-proBNP
  - thyroid and liver testing
  - complete blood cell count
  - pulmonary function testing
  - ventilation-perfusion scanning
  - sleep studies

✓ Diagnosis of DAH through use of BAL—progressively bloody return or elevated level of hemosiderin-laden macrophages (>20%) or both

✓ Anti-GBM disease—
  - typically younger male patients with Goodpasture syndrome and renal failure (pulmonary hemorrhage and rapidly progressive glomerulonephritis)
  - in older patients, glomerulonephritis alone
  - kidney biopsy: diffuse necrotizing crescentic glomerulonephritis
  - immunofluorescence staining: linear deposition of IgG and complement along basement membranes
  - treatment of choice: plasmapheresis (to remove circulating autoantibodies) and cyclophosphamide and systemic corticosteroids (to stop production of new autoantibodies)

✓ PAVMs—hypoxemia and paradoxical embolization complications (eg, TIA, stroke, and brain abscess)

✓ Pulmonary vascular tumors—breast, lung, prostate, pancreas, liver, and stomach cancers may metastasize to the pulmonary vasculature

Superior Vena Cava Syndrome

Superior vena cava (SVC) *syndrome* refers to any condition that leads to obstruction of the blood flow through the SVC. The obstruction can be caused by intraluminal occlusion (as seen in thrombosis of the vessel) or by extrinsic compression (as caused by abnormal growth of adjacent structures such as lymph nodes, mediastinal structures, or lung). The most common cause of SVC syndrome is malignancy. Non–small cell lung cancer, small cell lung cancer, and non-Hodgkin lymphomas are the most common causes of this syndrome. Other causes include thrombosis, fibrosing mediastinitis, and postradiation fibrosis. The most common signs and symptoms include dyspnea, facial swelling, head fullness, chest pain, dysphagia, cyanosis, and distention of the neck and upper thoracic veins. The most useful diagnostic study is contrast-enhanced computed tomography of the chest. Management is aimed at treating the cause of the obstruction (eg, anticoagulation for thrombosis, and chemotherapy or radiotherapy or both for malignancy). Endovascular stenting can improve the obstruction in selected patients, especially for palliation of symptoms in aggressive malignancies.

Pulmonary Lymphatic Disorders

Pulmonary lymphatic disorders include lymphangioma, lymphangiomatosis, lymphangiectasis, and pulmonary lymphatic dysplasia syndromes. Pulmonary lymphatic dysplasia syndromes include idiopathic lymphedema syndromes, idiopathic recurring chylous effusions, and yellow nail syndrome. They are characterized by obstruction of proximal lymphatic channels with a refractory accumulation of chyle. The immunoglobulin loss may result in immunodeficiency, and the protein loss may result in malnutrition. Yellow nail syndrome consists of lymphedema, yellow dystrophic nails, and idiopathic pleural effusions or respiratory tract illness (or both) with bronchiectasis and recurrent pneumonias. The nails usually do not grow, and patients may wonder why the nails do not need to be trimmed.

79

Sleep Disorders

MITHRI R. JUNNA, MD

Obstructive Sleep Apnea Disorders

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of upper airway obstruction during sleep with continued respiratory effort. An *apnea* is defined as cessation of airflow (duration ≥10 seconds) during sleep with *complete* obstruction of the upper airway and continued respiratory effort. Typically, the episode is terminated by a temporary arousal from sleep and return of normal upper airway patency. A **hypopnea** is defined as reduction of airflow (duration ≥10 seconds) during sleep with *partial* obstruction of the upper airway, usually with a resultant oxyhemoglobin desaturation of at least 4%, with continued respiratory effort. Typically a hypopnea is terminated by a temporary arousal from sleep. Such repetitive episodes of apnea and hypopnea usually result in periodic oxyhemoglobin desaturation and fragmented sleep. OSA should be suspected in those who snore or have witnessed apneas, in those who are obese or have increased neck circumference, and in those who complain of daytime sleepiness. An overnight in-laboratory polysomnogram or home sleep apnea test (HSAT) is required for making a diagnosis of OSA with documentation of 5 or more episodes of apnea and hypopnea per hour. Although overnight oximetry results may suggest the presence of OSA, oximetry is neither sensitive enough to rule out the diagnosis nor specific enough to confirm it.

Key Definition

Obstructive sleep apnea: *repetitive episodes of upper airway obstruction during sleep with continued respiratory effort.*

Key Definition

Hypopnea: *reduction of airflow (duration ≥10 seconds) during sleep with partial obstruction of the upper airway, usually with a resultant oxyhemoglobin desaturation of at least 4%, with continued respiratory effort.*

OSA has been associated with systemic dysfunction (Box 79.1). Several studies suggest that individuals with untreated OSA have an increase in perioperative complications and overall mortality.

Central Sleep Apnea Syndromes

Central sleep apnea (CSA) is characterized by repetitive episodes of complete (apnea) or partial (hypopnea) cessation of airflow (duration ≥10 seconds) during sleep without upper airway obstruction and without respiratory effort (presumably due to diminished central respiratory drive). In contrast to OSA, airflow in CSA is gradually resumed and is not always associated with a temporary arousal from sleep. CSA should be suspected in those who have witnessed apneas or complain of daytime sleepiness, particularly in the context of predisposing neurologic conditions (eg, stroke, Chiari malformations, or multiple system atrophy) or cardiovascular conditions (eg, congestive heart failure or atrial fibrillation). The respiratory pattern, which cycles between crescendo and decrescendo respirations followed by a pause, is known as *Cheyne-Stokes breathing* or *Cheyne-Stokes respiration* and typically occurs with congestive heart failure or after a stroke. CSA can also occur in association with renal failure, opiate use, or ascent to high altitude, and CSA may be idiopathic.

Box 79.1 • Systemic Disorders That Have Been Associated With Sleep-Related Breathing Disorders

- Central nervous system
    - Cognitive impairment
    - Excessive daytime sleepiness
    - Lower seizure threshold
    - Recurrent headaches
    - Stroke
- Cardiovascular system
    - Myocardial infarctions
    - Hypertension
    - Cardiac arrhythmias
    - Acceleration of atherosclerosis
    - Pulmonary hypertension
- Endocrine system
    - Insulin insensitivity
    - Suppression of growth hormone release
    - Alteration of progesterone and testosterone release
    - Obesity
- Digestive system
    - Gastroesophageal reflux disease
- Respiratory system
    - Hypercapnia
    - Dyspnea
    - Reduced exercise tolerance
- Psychiatric
    - Mood disorders
    - Insomnia

Key Definition

Central sleep apnea: *repetitive episodes of complete or partial cessation of airflow (duration ≥10 seconds) during sleep without upper airway obstruction and without respiratory effort (presumably due to diminished central respiratory drive).*

Sleep-Related Hypoventilation Disorders

Sleep-related hypoventilation is characterized by decreased minute ventilation with resultant hypercapnia and usually hypoxemia during sleep. Affected individuals may also have daytime hypoventilation with resultant hypercapnia, pulmonary hypertension, cor pulmonale, and neurocognitive dysfunction. Most affected individuals are obese (*obesity-hypoventilation syndrome*) or have severe respiratory or neurologic disease.

Sleep-Related Hypoxemia Disorder

Sleep-related hypoxemia is characterized by hypoxemia during sleep that is not explained by OSA or CSA or sleep-related hypoventilation. Affected individuals may also have daytime hypoxemia, pulmonary hypertension, and cor pulmonale.

Treatment of Sleep-Related Breathing Disorders

Individuals with OSA are treated with noninvasive positive pressure devices, such as continuous positive airway pressure and bilevel positive airway pressure (BPAP) devices. Adequate titration can be achieved during in-laboratory polysomnography, but in certain circumstances, an autotitrating positive airway pressure (PAP) device may be used. Alternatives to PAP therapy can include avoidance of supine sleep (if applicable), oral appliance therapy, oral pressure therapy, surgical treatments, and placement of a hypoglossal nerve stimulator. In severe cases, tracheostomy may be required. Treatment of CSA usually requires a specialized BPAP device known as an adaptive servo-ventilator. Treatment of obesity-hypoventilation syndrome includes weight loss and the use of a BPAP device. Individuals with isolated sleep-related hypoxemia disorder may benefit from the use of supplemental oxygen therapy.

KEY FACTS

✓ Typical features of patients with OSA—obesity, large neck circumference, history of snoring, and complaints of daytime sleepiness

✓ Diagnosis of OSA—

- overnight in-laboratory polysomnogram or HSAT
- ≥5 episodes of apnea and hypopnea per hour

✓ Causes of CSA—

- neurologic conditions (eg, stroke, Chiari malformations, or multiple system atrophy)
- cardiovascular conditions (eg, congestive heart failure or atrial fibrillation)
- renal failure
- opiate use
- high altitude
- idiopathic

✓ Treatment of OSA—if severe, may require tracheostomy

✓ Treatment of CSA—usually requires a specialized BPAP device (an adaptive servo-ventilator)

Insomnia

Insomnia is characterized by difficulties with sleep initiation, sleep maintenance, or sleep quality despite adequate opportunity for sleep. Consequent daytime dysfunction can include fatigue or sleepiness, depressed mood or irritability, or cognitive difficulties. An inadequate opportunity for sleep may be related to poor sleep hygiene or environmental sleep disruptions, which should be addressed to aid with sleep difficulties. Furthermore, the presence of a comorbid sleep disorder (eg, restless legs syndrome or sleep-disordered breathing) or a comorbid disorder other than a sleep disorder (eg, drug or substance use or psychiatric condition) should be identified and treated to improve sleep. The use of cognitive behavioral therapy for insomnia (CBT-I) and sedative hypnotic therapy can be helpful, although sedative hypnotic therapy should be used with caution, particularly in the elderly, because of an increased propensity for adverse effects.

Key Definition

Insomnia: *difficulty with sleep initiation, maintenance, or quality despite adequate opportunity for sleep.*

Parasomnias

Parasomnias are undesirable sensory or motor experiences that occur while falling asleep, sleeping, or arousing from sleep. These experiences can be disruptive to the individual or bed partner and may pose a safety concern. They are generally classified by the state of sleep from which they arise and include non–rapid eye movement (NREM) disorders of arousal (NREM parasomnias), rapid eye movement (REM) parasomnias, and other parasomnias.

Key Definition

Parasomnia: *an undesirable sensory or motor experience that occurs while falling asleep, sleeping, or arousing from sleep.*

Sleepwalking is a type of NREM parasomnia characterized by complex and coordinated motor behaviors that often include walking. Generally a childhood disorder, it may persist into adulthood and occur in association with the use of sedative hypnotics. The presence of a comorbid sleep disorder such as sleep-disordered breathing should be identified and treated to reduce the propensity for behaviors to occur. Treatment includes avoidance of precipitating factors (eg, environmental disruption, alcohol use, or sleep deprivation), awareness of bedroom safety, and consideration for the use of certain benzodiazepines.

REM sleep behavior disorder is a type of REM parasomnia characterized by vocalizations and complex motor behaviors occurring in association with a dream. It may be seen with antidepressant exposure, certain neurodegenerative disorders (eg, Parkinson disease, dementia with Lewy bodies, or multiple system atrophy), brainstem lesions, or certain autoimmune neurologic conditions. In-laboratory polysomnography demonstrates increased muscle tone during REM sleep and dream-enactment behaviors. Treatment includes identification and management of a comorbid sleep disorder such as sleep-disordered breathing, awareness of bedroom safety, and consideration for use of melatonin or clonazepam (or both).

Restless Legs Syndrome

Restless legs syndrome is characterized by an urge to move the legs that may be accompanied by an uncomfortable sensation. The symptoms generally occur during periods of rest or inactivity and improve with movement. They tend to be worse in the evening and night. The symptoms should not be better explained by other conditions (eg, arthralgias, cramps, positional discomfort, myalgias, or neuropathy). Accompanying leg jerks or kicks, which may occur during wakefulness or sleep, are referred to as *periodic limb movements*. The disorder can lead to difficulties with sleep initiation or maintenance and consequent daytime dysfunction. It may be seen in association with pregnancy, renal failure, iron deficiency, or the use of certain medications (eg, antidepressants, neuroleptics, dopamine-blocking antiemetics, and sedating antihistamines). Treatments include iron replacement (if applicable) and pharmacologic management with the use of non–ergot-derived dopamine agonists or alpha-2-delta calcium channel ligands. Opiates may need to be considered in refractory cases.

KEY FACTS

- ✓ Insomnia—CBT-I and sedative hypnotic therapy can be helpful
- ✓ Sleepwalking—an NREM parasomnia that may involve a comorbid sleep disorder (eg, sleep-disordered breathing)
- ✓ REM sleep behavior disorder—an REM parasomnia in which vocalizations and complex motor behaviors occur with a dream
- ✓ Restless legs syndrome—symptoms usually occur during periods of rest or inactivity, tend to be worse in the evening and night, and improve with movement

XII

Questions and Answers

Questions

Multiple Choice (Choose the best answer)

XII.1. A 64-year-old man who has never smoked has had shortness of breath for the past 6 days. He is given 100% oxygen with a simple mask, but his oxygen saturation level remains low. Radiography of the chest shows consolidation of the right focal upper lobe. He is intubated, and mechanical ventilation is begun. Arterial blood gas testing shows that his $Pa\text{O}_2$ is 145 mm Hg while receiving 50% inspired oxygen with positive end-expiratory pressure (PEEP) set at 5 cm H_2O. Which finding in this patient is *inconsistent* with acute respiratory distress syndrome (ARDS)?

a. Duration of symptoms
b. Nonsmoker
c. Focal infiltrate
d. Ratio of $Pa\text{O}_2$ to fraction of inspired oxygen ($F\text{IO}_2$)

XII.2. A 32-year-old woman presents with a 1-day history of a red rash that started on her right hand and has spread toward her elbow. Family members report that her behavior is atypical, and they are frustrated that the patient seems inappropriately unconcerned about her arm rash. On examination, her pain extends beyond a red area on her hand and forearm. She has an abrasion on her right hand. Her pulses are intact. Crepitus is absent. Her temperature is 38°C, her heart rate is 119 beats per minute, her blood pressure is 89/48 mm Hg, and her respiratory rate is 26 breaths per minute. She does not obey commands, but she does open her eyes when her arm is examined, and she tries to withdraw it. No other focal findings are apparent from her examination. Her laboratory values are notable for the following: creatinine 2.3 mg/dL; hemoglobin 7.2 g/dL; white blood cell count 26×10^9/L; platelet count 93×10^9/L; glucose 170 mg/dL; bilirubin 2.3 mg/dL; and lactate 3 mmol/L. What is the most appropriate next step for this patient?

a. Administer 2 units of insulin subcutaneously.
b. Administer vasopressin intravenously to maintain a mean arterial blood pressure of at least 65 mm Hg.
c. Transfuse 2 units of packed red blood cells.
d. Obtain samples for blood cultures.

XII.3. A 52-year-old man is brought to the emergency department by his family with complaints of being "intoxicated" and ataxic and having garbled speech. He also had nausea and vomiting. The family reported that he was under a lot of stress and has been drinking heavily for several days. On physical examination his blood pressure was 105/68 mm Hg, his heart rate was 120 beats per minute, his respiratory rate was 22 breaths per minute, and his oxygen saturation was 97% with room air. The rest of the physical examination findings were unremarkable. Initial laboratory test results are shown in Table XII.Q3.
Which alcohol did the patient most likely ingest?

a. Ethanol
b. Ethylene glycol
c. Isopropyl alcohol
d. Methanol

Table XII.Q3.

Component	Finding
pH	7.32
$P\text{CO}_2$, mm Hg	27
$P\text{O}_2$, mm Hg	96
Lactate, mmol/L	15.5
Sodium, mmol/L	143
Potassium, mmol/L	3.3
Chloride, mmol/L	106
Bicarbonate, mmol/L	15
Serum urea nitrogen, mg/dL	28
Creatinine, mg/dL	2.6
Glucose, mg/dL	72
Blood alcohol, mg/dL	18.5
Ketones in urine (dipstick testing)	Negative
Measured serum osmolality, mmol/kg	322

XII.4. A 38-year-old man presented with a 3-day history of fever, productive cough, and right-sided chest pain. He was in moderate respiratory distress. Chest radiography showed a large right lower lobe pneumonia and slight blunting of the right costophrenic angle. He was admitted to the hospital and administered intravenous antibiotics after blood samples were obtained for cultures. His symptoms appeared to improve, but on hospital day 3, he had an increased fever and white blood cell count. Follow-up radiography of the chest showed a moderate right-sided pleural effusion. Ultrasonographically guided thoracentesis showed a few loculations with drainage of 500 mL of an amber-colored fluid. Fluid analysis confirmed the following: pH 7.1, glucose 58 mg/dL, and LDH 500 U/L; Gram staining was negative. What is the most likely diagnosis and the best next step in management?

a. Uncomplicated parapneumonic effusion; thoracentesis-based drainage
b. Empyema; consultation with thoracic surgery staff for operative decortication
c. Complicated parapneumonic effusion; insertion of a pigtail catheter or small-bore chest tube with administration of tissue plasminogen activator (tPA) and deoxyribonuclease (DNase)
d. Complicated parapneumonic effusion; insertion of a large-bore chest tube

XII.5. A 67-year-old man with end-stage liver disease (cirrhosis) from nonalcoholic steatohepatitis presents with dyspnea and a large right-sided pleural effusion. This is his third presentation with a large right-sided effusion in the past 6 months. On examination, the patient has tense ascites, spider nevi, and gynecomastia. On thoracentesis, he again has a pale-yellow, clear fluid with pH 7.4, glucose 100 mg/dL, protein 1.2 g/dL, and lactate dehydrogenase (LDH) 60 U/L. Lipid analysis results are normal. On a previous workup, the patient had a normal echocardiogram, normal renal function, and normal thyrotropin level. What is the likely cause of this patient's effusion?

a. Hepatic hydrothorax
b. Congestive heart failure
c. Hypoalbuminemia
d. Chylothorax

XII.6. A 67-year-old man with known bilateral lower lobe bronchiectasis presents to his primary care physician to establish care. The patient has had 3 exacerbations of bronchiectasis in the past year. These have been treated with oral antibiotics on each occasion, but he has not required hospitalization. Lung function testing over the past 2 years has shown progressive obstruction, with forced expiratory volume in the first second of expiration currently at 55% of the predicted value. His current bronchiectasis regimen includes nebulized hypertonic saline (7%) twice daily and then use of a chest vibratory device to facilitate secretion expectoration. What is the best next step in the management of this patient?

a. Add doxycycline 100 mg twice daily for the first 10 days of each month.
b. Add daily oral azithromycin.
c. Continue current management.
d. Add nebulized dornase alfa.

XII.7. A 50-year-old woman presented with cough, dyspnea, and diffuse pulmonary infiltrates that had persisted for 3 months despite multiple courses of oral antibiotics. Computed tomography of the chest showed peripheral-predominant ground-glass and consolidated opacities. Bronchoscopy was performed. Bronchoalveolar lavage was negative for pathogenic organisms, and histopathology from transbronchial lung biopsies showed organizing pneumonia. An underlying cause was not identified, and the diagnosis was cryptogenic organizing pneumonia (COP). Systemic corticosteroid therapy was initiated, and the symptoms resolved rapidly. After 6 months of treatment, the corticosteroids were tapered. Shortly thereafter, cough and dyspnea returned, and chest radiography showed a return of pulmonary infiltrates. What is the best next step in management?

a. Performing a surgical lung biopsy
b. Initiating treatment with a corticosteroid-sparing immunosuppressive agent
c. Restarting systemic corticosteroid therapy
d. Treating with a short course of oral antibiotics

XII.8. A 35-year-old man presents for evaluation of cough, which has been persistent over the past 6 months. He is a lifelong nonsmoker, and his past medical history is notable only for hypertension, managed with amlodipine and lisinopril. He reports no fever, rash, or joint symptoms. Radiography of the chest shows bilateral hilar lymphadenopathy and upper lobe–predominant nodular pulmonary infiltrates. What is the most likely diagnosis for this patient?

a. Idiopathic pulmonary fibrosis (IPF)
b. Drug-induced interstitial lung disease (ILD)
c. Lisinopril-associated cough
d. Sarcoidosis

XII.9. A 30-year-old woman who has never smoked presents to the emergency department with acute-onset chest pain and shortness of breath. Chest radiography shows a right-sided pneumothorax. After a chest tube is placed, computed tomography (CT) of the chest shows well-defined cysts scattered diffusely throughout both lungs without associated nodules or interstitial fibrosis. What is the best next step in treatment of this patient?

a. Tamoxifen
b. Prednisone
c. Sirolimus
d. Methotrexate

XII.10. A 58-year-old woman with a 100-pack-year history of smoking presents to her primary care clinic for follow-up after she was recently hospitalized for dyspnea and mucopurulent cough. She reports having 2 similar episodes in the past year. Her forced expiratory volume in the first second of expiration is 40% of the predicted value with an obstructive pattern. A chest radiograph is normal. The review of systems is positive for a productive cough that has been ongoing for the past 3 years. The patient typically expectorates about a teaspoon of white-yellow phlegm every morning and a similar amount through the rest of the day. Her chronic obstructive pulmonary disease (COPD) inhaler regimen consists of once-daily umeclidinium bromide–vilanterol and twice-daily budesonide. What are the most appropriate diagnosis and therapy for this patient?

a. Severe COPD with chronic bronchitis; initiation of inhaled tiotropium
b. COPD with bronchiectasis; initiation of doxycycline for the first 10 days of each month

c. Severe COPD; continuation of current therapy
d. COPD with chronic bronchitis; initiation of oral roflumilast

XII.11. A 67-year-old man (currently a nonsmoker) with severe chronic obstructive pulmonary disease (COPD) presents to the emergency department with a 3-day history of increasing shortness of breath, a low-grade fever, and new mucopurulent sputum production. Chest radiography shows some hyperinflation. He reports having 2 such episodes in the past 12 months, but he reports that he did not have a productive cough between these episodes. In moderate respiratory distress, he is admitted to the hospital and administered supplemental oxygen, oral prednisone (40 mg once daily), oral levofloxacin, and nebulized bronchodilator therapy. Home COPD therapy consists of inhaled tiotropium along with a salmeterol-fluticasone combination inhaler. What additional therapy would be the most appropriate to consider for this patient on discharge?

a. Prescribing azithromycin 250 mg once daily
b. Discontinuing the inhaled corticosteroid (fluticasone) because of frequent episodes of pneumonia
c. Continuing the current therapy without any changes
d. Enrolling the patient in a COPD rehabilitation program

XII.12. A 70-year-old man presents for evaluation of chronic obstructive pulmonary disease (COPD). He wonders whether he would benefit from supplemental oxygen. A resting arterial blood gas analysis shows a P_{O_2} of 57 mm Hg and a corresponding oxygen saturation as measured by pulse oximetry (S_{PO_2}) of 90%. Echocardiography shows normal right ventricular function with a right ventricular systolic pressure of 34 mm Hg. Hemoglobin is 13.8 g/dL, and the patient has no signs of heart failure (no lower extremity edema or dilated neck veins). What should this patient be told about the utility of supplemental oxygen?

a. Start long-term oxygen therapy (LTOT) with a target S_{PO_2} of at least 90%.
b. Do not start LTOT because it provides no proven benefit in this situation.
c. Continue the current therapy without any changes.
d. The patient should be enrolled in a pulmonary rehabilitation program.

XII.13. A 38-year-old man presents to the emergency department with sudden onset of dyspnea and sharp right-sided chest pain after a fall from a ladder. He is seated in a semirecumbent position. His oxygen saturation as measured by pulse oximetry is 94% (with room air), his respiratory rate is 22 breaths per minute, and his blood pressure is 124/86 mm Hg. A portable x-ray machine was used for a radiograph of the chest (Figure XII.Q13).

What is the diagnosis and the best next step in the management of this patient?

a. Right-sided pneumothorax; insertion of a pigtail catheter
b. Right-sided pneumothorax; insertion of a large-bore chest tube
c. Right-sided pneumothorax; hospitalization for observation
d. Right-sided pneumonia; hospitalization and administration of antibiotics

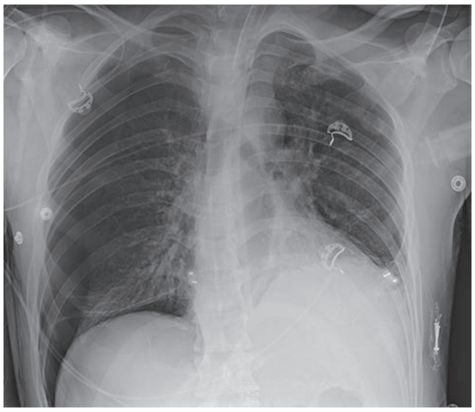

Figure XII.Q13

XII.14. A 56-year-old obese, nonsmoking woman with a history of hypertension that is difficult to control presents with a 6-month history of chronic cough. Her primary physician recently added 2 new medications for her hypertension. She describes her cough as dry and nonproductive with no particular daytime or nocturnal predominance. She describes an itch or tickle in her throat that seems to trigger her cough. She does not describe any clinical features that would suggest asthma or gastroesophageal reflux disease (GERD). Results from pulmonary function testing and radiography of the chest were within normal limits. What is the best next step in the management of this patient?

a. Empirical therapy for postnasal drainage given the patient's throat tickle
b. Omeprazole 20 mg twice daily because silent GERD is present in 20% of patients with chronic cough
c. Careful reconciliation of the patient's medication list
d. Computed tomography (CT) of the chest to evaluate for intrathoracic malignancy

XII.15. A 58-year-old man presents with dyspnea that has been progressively worsening over the past 2 years. He does not report a cough or other constitutional symptoms. He has never smoked, but he does report some secondhand smoke exposure at his workplace. There are no other environmental or occupational exposures of concern. The flow-volume curve from spirometry (with forced expiratory time [FET]) is shown in Figure XII.Q15 (next page). Forced expiratory volume in the first second of expiration (FEV_1) was 2.1 L (55% of predicted).

A chest radiograph was consistent with hyperinflation, and follow-up computed tomography of the chest showed panacinar emphysema with lower lobe predominance. What is the diagnosis and likely cause?

a. Moderate obstruction due to idiopathic emphysema
b. Moderate obstruction due to α_1-antitrypsin deficiency
c. Moderate obstruction due to second-hand smoke exposure
d. Severe chronic bronchitis due to second-hand smoke exposure

XII.16. A 48-year-old woman with newly diagnosed alcoholic liver cirrhosis is evaluated after a recent admission for esophageal varices bleeding that resolved after variceal banding. The patient's oxygen saturation as measured by pulse oximetry was 86% while breathing room air. She does not have any respiratory symptoms and denies dyspnea, chest pain, cough, and wheezing. She is a nonsmoker and has no history of cardiac or pulmonary disease. Physical examination findings are remarkable only for mild ascites and digital clubbing. Radiography of the chest (posteroanterior and lateral views) is unremarkable; arterial blood gas results were Pa_{O_2} 58 mm Hg, normal P_{CO_2}, and normal acid-base status.

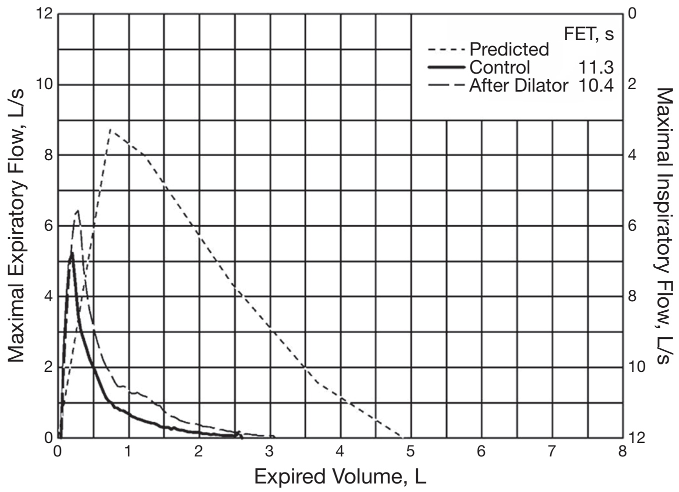

Figure XII.Q15

What is the best next step to identify the cause of this patient's hypoxemia?

a. Noncontrast computed tomography (CT) of the chest
b. Contrast-enhanced echocardiography (bubble study)
c. Spirometry
d. Bronchoscopy for bronchoalveolar lavage

XII.17. A 62-year-old man with a known history of granulomatosis with polyangiitis is admitted because of worsening dyspnea, mild fever, and productive cough with bloody specks over the past 3 days. He is known to be positive for cytoplasmic antineutrophil cytoplasmic antibody (ANCA) and proteinase 3 and has been receiving maintenance therapy (azathioprine 150 mg daily and prednisone 5 mg daily) for approximately 1 year. He has no known history of cardiac disease and is not receiving anticoagulants or antiplatelet agents. He visited his rheumatologist 2 months ago and was told that his disease was in complete remission. He was found to be tachycardic and hypoxemic (84% oxygen saturation as measured by pulse oximetry while breathing room air). The hypoxemia improved with oxygen supplementation. On lung auscultation, the patient had bilateral fine crackles; all other physical examination findings were normal. Radiography of the chest showed bilateral diffuse infiltrates with no pleural effusions and no cardiomegaly. His blood test results were remarkable for low hemoglobin (9 g/dL), which was decreased from 2 months ago when he visited his rheumatologist (13.8 g/dL); the C-reactive protein level and the erythrocyte sedimentation rate were considerably elevated; renal function was normal, and the N-terminal pro-brain natriuretic peptide level was normal. What is the best next diagnostic test to identify this patient's respiratory problem?

a. Bronchoscopy for bronchoalveolar lavage
b. Computed tomography (CT) of the chest
c. Echocardiography
d. Ventilation-perfusion study

XII.18. A 60-year-old woman with known systemic sclerosis (scleroderma) is evaluated because she has had progressive dyspnea for 8 months. Her main scleroderma symptoms have been dysphagia and Raynaud phenomenon, but otherwise she has been fairly asymptomatic. Her vital signs are normal, including oxygen saturation as measured by pulse oximetry of 98% in room air, and the physical examination findings are remarkable for only sclerodactyly and an increased second pulmonic sound on cardiac auscultation. Noncontrast computed tomography of the chest showed mildly prominent pulmonary arteries. Results from complete pulmonary function testing, including lung volumes, spirometry, and diffusing capacity of lung for carbon monoxide, were unremarkable. Echocardiography was notable for an elevated right ventricular systolic pressure of 55 mm Hg with mild right ventricular enlargement but normal right and left ventricular function. What is the best next diagnostic test for determining the cause of this patient's progressive dyspnea?

a. Arterial blood gas analysis
b. Treadmill cardiac stress test
c. Methacholine challenge test
d. Right heart catheterization

XII.19. A 52-year-old man presents with a history of snoring, witnessed apneas, and excessive daytime sleepiness. On examination, his blood pressure is elevated at 152/90 mm Hg, his body mass index is 38 kg/m^2, his neck circumference is 44 cm, and he has a crowded oropharynx. What is the best next step in management of this patient?

a. Overnight oximetry
b. Home sleep apnea test (HSAT)
c. Use of a 24-hour ambulatory blood pressure monitor
d. Tilt-table test

XII.20. A 34-year-old woman presents with a history of an uncontrollable urge to move her legs, which occurs nightly while lying in bed. Stretching her legs and walking offer temporary symptomatic relief, although sleep initiation is affected. She provides a history of heavy menstrual periods. Neurologic examination findings are normal for the lower limbs, including motor strength, reflexes, and sensation to vibration, joint position, pinprick, and temperature. What is the best next step in management of this patient?

a. Vitamin B_{12}
b. Magnesium
c. Ferritin
d. Creatine kinase

XII.21. A 67-year-old man presents with a 10-year history of nocturnal vocalizations and movements that occur on most nights during a dream, with occasional falls out of bed due to the movements. On examination, he has a slowed and stooped posture while walking and a diminished arm swing. Which of the following can occur in association with the suspected diagnosis?

a. Alzheimer dementia
b. Amyotrophic lateral sclerosis
c. Multiple system atrophy
d. Frontotemporal dementia

Answers

XII.1. Answer c.

ARDS is a diffuse lung injury that causes acute hypoxic respiratory failure in less than 1 week. The 6-day duration of symptoms fits the diagnosis of ARDS, which can occur in smokers or nonsmokers. Patients with ARDS present with bilateral opacities and hypoxia that are not otherwise explained, and when PEEP is set at 5 cm H_2O or more, the Pa_{O_2}:F_{IO_2} ratio is 300 cm H_2O or less.

XII.2. Answer d.

The patient's clinical presentation of a rapidly spreading skin infection is worrisome for necrotizing fasciitis, which often occurs as a rapidly spreading, painful area that typically has skin changes such as redness, blisters, or necrosis. Crepitus need not be present. In severe cases, patients may have compartment syndrome and anesthesia. They may also present with la belle indifference—a change in mental status with an inappropriate lack of concern for the infection. This patient's vital signs and laboratory findings in the presence of infection are consistent with sepsis. She has organ dysfunction; her calculated Sequential Organ Failure Assessment score would be 9 (predicted mortality, 40%-50%). She should receive 30 mL/kg of intravenous crystalloid. If she remains hypotensive despite volume resuscitation, she would meet the criteria for septic shock. In sepsis, blood glucose should be maintained no higher than 180 mg/dL. The patient should receive a rapid bolus of fluid before vasopressors. In addition, norepinephrine is recommended as the vasopressor of choice in sepsis. Vasopressin can be added if a second agent is needed. The transfusion threshold should be a hemoglobin level less than 7 g/dL in the absence of active ischemia or bleeding. Recommendations include obtaining samples for blood cultures before administering antibiotics and beginning empirical broad-spectrum antibiotic therapy within 1 hour after sepsis recognition.

XII.3. Answer b.

Ethylene glycol is found in antifreeze and solvents. The diagnosis of ethylene glycol toxicity should be suspected when a patient has an anion gap metabolic acidosis and an increased osmolar gap. This patient has an elevated anion gap of 22 mmol/L, calculated as sodium – (chloride + bicarbonate). The calculated serum osmolality is 305 mmol/kg, calculated as (2 × sodium) + (serum urea nitrogen/2.8) + (glucose/18) + (ethanol/3.7). The patient has an osmolal gap of 17 mmol/L. The serum lactate of 15.5 mmol/L is higher than expected from the magnitude of increase in the anion gap because of falsely elevated lactate due to cross-reactivity of glycolate. Isopropyl alcohol ingestion would not explain the presence of an elevated anion gap or renal dysfunction. Furthermore, the absence of ketones in the urine makes isopropyl alcohol less likely. Methanol ingestion can present like ethylene glycol intoxication except that methanol does not cause markedly elevated lactate. In addition, ethylene glycol is associated with renal toxicity, whereas methanol is associated with vision changes. Ethanol intoxication is unlikely because the urine was negative for ketones, the alcohol level was not markedly elevated, and the lactate levels were inappropriately high.

XII.4. Answer c.

The clinical presentation is consistent with a complicated parapneumonic effusion (low pH, low glucose, and presence of loculations). The best approach to adequately drain this effusion is the administration of intrapleural tPA and DNase through a small-bore chest tube or pigtail catheter. The presence of pus or extensive loculations would necessitate the use of a large-bore catheter to ensure adequate drainage. This effusion would not be classified as uncomplicated given the low pH and low glucose. An empyema is diagnosed when frank pus is aspirated or when the Gram stain or pleural fluid cultures are positive.

XII.5. Answer a.

The presentation is consistent with hepatic hydrothorax (recurrent large transudative pleural effusions in a patient with cirrhosis and no alternative explanation). Hepatic hydrothorax occurs predominantly on the right side and is transudative. Treatment is focused on controlling the ascites, which can become an intractable problem. The normal echocardiogram excludes congestive heart failure. Hypoalbuminemia-related effusions are typically bilateral with associated anasarca. Chylothorax is unlikely given the normal results from lipid analysis of the pleural fluid.

XII.6. Answer b.

This patient presents with bronchiectasis and a history of frequent exacerbations (≥2 exacerbations in 12 months). The addition of oral azithromycin in this situation has been shown to markedly reduce the frequency of exacerbations, but its effect on lung function or quality of life is less certain. Addition of doxycycline on a scheduled basis for the first 10 days of each month may be a useful option if it is rotated with other antibiotics on a monthly basis. Use of a single agent such as doxycycline for a prolonged period is likely to result in drug resistance. Continuing current therapy without making any changes does not address the patient's history of frequent exacerbations. Dornase alfa is not effective for non–cystic fibrosis bronchiectasis and is not recommended in this situation.

XII.7. Answer c.

The patient has had a rebound of disease activity after completion of 6 months of treatment with systemic corticosteroids for management of COP. Such rebounds are common in the management of COP and are initially managed by extending the duration of systemic corticosteroid treatment. Both the initial favorable response to corticosteroids and the difficulty encountered in tapering the treatment provide clinical confirmation of the diagnosis of COP, and so a surgical lung biopsy is not indicated. A corticosteroid-sparing immunosuppressive agent is rarely necessary for treatment of COP and should not be introduced at this relatively early point in the patient's course. Although bacterial pneumonia is a diagnostic consideration, a rebound of COP is much more likely in this scenario, and so a short course of oral antibiotics is unlikely to prove effective.

XII.8. Answer d.

Although the differential diagnosis remains fairly broad from the information provided, sarcoidosis is the most likely consideration among the answer choices. Sarcoidosis is compatible with the history of cough in a lifelong nonsmoker in his fourth decade, and the radiographic findings of bilateral hilar lymphadenopathy and upper lobe–predominant infiltrates would be typical for stage II pulmonary sarcoidosis. IPF would be unlikely in someone so young (it usually affects persons older than 50 years), and the radiographic abnormalities of IPF typically predominate in the lower lobes. Neither amlodipine nor lisinopril is associated with drug-induced ILD, and a patient with lisinopril-associated cough should not have abnormalities on chest imaging.

XII.9. Answer c.

The patient most likely has lymphangioleiomyomatosis (LAM), a cystic lung disease that affects women of childbearing age who often present with spontaneous pneumothorax. The CT findings are classic for LAM: The dominant feature is well-defined pulmonary cysts that are diffusely distributed throughout both lungs without associated nodules or interstitial fibrosis. Sirolimus is the first-line medical therapy for stabilization of LAM. Tamoxifen and other treatments directed at hormonal manipulation have little evidence to support their use, and are not recommended for the treatment of LAM. Prednisone and methotrexate are not used for LAM.

XII.10. Answer d.

The patient's clinical features are consistent with a diagnosis of chronic bronchitis (≥3 months of productive cough for 2 consecutive years). For COPD patients who have chronic bronchitis and frequent exacerbations despite maximal inhaler therapy, the addition of roflumilast (a phosphodiesterase-4 inhibitor) is beneficial. Roflumilast is associated with a 15% to 20% reduction in the risk of moderate-severe COPD exacerbations in patients with chronic bronchitis. Adding tiotropium is not advisable because the patient is already receiving a long-acting muscarinic antagonist (umeclidinium). This patient does not have bronchiectasis because the chest radiograph was normal and the volume of sputum is small. Continuing the current therapy would not reduce her future risk of COPD exacerbations.

XII.11. Answer a.

The patient's presentation is consistent with an acute exacerbation of COPD. Given that the patient has had 2 similar episodes in the past, the exacerbations would be classified as frequent (≥2 exacerbations in the preceding 12 months). Azithromycin has been shown to reduce the frequency of exacerbations and should be initiated after a discussion with the patient and medication reconciliation. Risks of long-term azithromycin therapy include hearing and vestibular disturbances and potential increases in drug-resistant pathogens. Although use of inhaled corticosteroids has been associated with an increased risk of pneumonia, this patient had a normal chest radiograph without pneumonia, and discontinuation of inhaled corticosteroids is not recommended. Enrollment in a COPD rehabilitation program is a worthy goal, but it would not directly address the frequent COPD exacerbations in this patient.

XII.12. Answer b.

A recent clinical trial, the Long-Term Oxygen Treatment Trial, confirmed the lack of mortality benefit in COPD patients, like this patient, who had a moderate degree of hypoxemia. Patients in this trial had a resting Spo_2 of 89% to 93% and were randomly assigned in a 1:1 fashion to receive 24-hour supplemental oxygen or no supplemental oxygen. After a median follow-up of 18 months, the supplemental oxygen group did not have a mortality benefit. On the basis of this trial, supplemental oxygen is recommended only for patients with a Pao_2 of 55 mg/Hg or less or a resting Spo_2 of 88% or less. Continuing the current therapy or enrolling the patient in a pulmonary rehabilitation program does not address the primary question of whether to start supplemental oxygen for this degree of hypoxemia.

XII.13. Answer a.

This patient presents with a large right-sided pneumothorax with mild respiratory distress but no obvious signs of hemodynamic compromise or mediastinal shift (ie, no signs of tension pneumothorax). This patient can be managed adequately with a pigtail catheter and an underwater seal. A large-bore chest tube would have been appropriate for a patient with tension pneumothorax or with concurrent hemothorax. Hospital admission and observation alone are not appropriate for a patient who has tachypnea and a large pneumothorax.

XII.14. Answer c.

The patient's medication list should be reconciled given her history of hypertension and the possibility that an angiotensin-converting enzyme (ACE) inhibitor may have been added recently. ACE inhibitor–related cough occurs in 2% to 10% of patients and is typically dry and resolves within 1 to 4 weeks after drug discontinuation. Postnasal drainage can be silent in some patients, but the first step in this patient's management is medication reconciliation. Empirical GERD therapy in the absence of classic GERD symptoms (heartburn or water brash) is discouraged. CT of the chest for an otherwise low-risk patient (nonsmoker) with a normal chest radiograph is low yield and not recommended.

XII.15. Answer b.

The patient has moderate emphysema ($50\% \le FEV_1 < 80\%$) likely due to α_1-antitrypsin deficiency. Smoking-related emphysema typically involves the upper lobe, whereas α_1-antitrypsin deficiency typically involves the lower lobes with a panacinar distribution. The first step in diagnosis is to quantitate serum α_1-antitrypsin levels and then perform genotype analysis to confirm the diagnosis. Treatment involves replacing the α_1-antitrypsin with 1 of the 4 products approved by the US Food and Drug Administration for this indication. This patient's secondhand smoke exposure is not enough to account for the airflow obstruction or the lower lobe predominance of the emphysema. This patient does not complain of cough, and the diagnosis of chronic bronchitis requires the presence of at least 3 months of productive cough for at least 2 consecutive years.

XII.16. Answer b.

Hepatopulmonary syndrome (HPS) is the most likely cause of this patient's hypoxemia. Contrast-enhanced echocardiography (bubble study) is necessary to identify intrapulmonary vascular dilatations, which are part of the diagnostic criteria of HPS. The other 2 criteria are portal hypertension and hypoxemia at rest; both are present in this patient. Noncontrast CT of the chest is unlikely to show abnormalities that could explain the hypoxemia because this patient does not have respiratory symptoms, lung examination findings were normal, and radiographs of her chest were normal. Spirometry and bronchoscopy are also unlikely to be useful for identifying abnormalities that could explain hypoxemia in an asymptomatic patient with normal findings on chest imaging and lung examination.

XII.17. Answer a.

This patient with ANCA-associated vasculitis is likely presenting with diffuse alveolar hemorrhage. Bronchoscopy for bronchoalveolar lavage is indicated to confirm the diagnosis by showing progressively bloody return or an elevated number of hemosiderin-laden macrophages or both. In addition, bronchoscopy is important for excluding infection in an immunocompromised patient who presents with pulmonary infiltrates and respiratory symptoms. CT of the chest could be used to confirm the radiographic findings, but it cannot be used to clearly distinguish the cause of the diffuse infiltrates. Echocardiography would be of limited value because heart failure seems unlikely with this patient's clinical presentation. A ventilation-perfusion study is also of limited value because this clinical presentation is unlikely to be related to acute pulmonary embolism.

XII.18. Answer d.

The patient's progressive dyspnea is most likely secondary to pulmonary arterial hypertension (PAH), which is a known pulmonary complication of patients with scleroderma. The definitive diagnostic test for PAH is right heart catheterization to prove elevation of the mean pulmonary artery pressure and pulmonary vascular resistance in the presence of normal pulmonary arterial wedge pressure. Arterial blood gas analysis is unnecessary because the patient is not hypoxemic and a hypoventilatory problem is unlikely. Coronary artery disease is also unlikely, so a cardiac stress test does not seem to be indicated. The methacholine challenge test is a bronchoprovocation test for evaluating airway hyperreactivity in patients who have asthma, which seems unlikely in this patient.

XII.19. Answer b.

The patient has a history and examination findings that suggest obstructive sleep apnea. Therefore, of the answers provided, HSAT would be the most appropriate test to confirm the diagnosis. Overnight oximetry may be used as a screening tool but is neither sensitive enough to rule out the diagnosis nor specific enough to confirm it. The other 2 tests are not used to make a diagnosis of obstructive sleep apnea.

XII.20. Answer c.

The patient has a history that is consistent with restless legs syndrome. Of the answer choices provided, ferritin would be the most appropriate test, particularly in the context of heavy menstrual periods. The other tests are not appropriate under these circumstances, especially given the normal findings on neurologic examination.

XII.21. Answer c.

The patient has a history to suggest rapid eye movement sleep behavior disorder (RBD) with findings of parkinsonism on examination. Of the choices listed, multiple system atrophy is a synucleinopathy that can occur in association with RBD. The other conditions are not synucleinopathies and are not associated with RBD.

Section

XIII

Rheumatology

80

Connective Tissue Diseases

FLORANNE C. ERNSTE, MD

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of unknown cause that affects multiple organ systems. SLE has a wide range of heterogeneous clinical manifestations and is characterized by disease flares and remissions. Disease severity covers a broad spectrum, leading to serious morbidity and an increased mortality rate.

Key Definition

Systemic lupus erythematosus: *a chronic, inflammatory autoimmune disease of varying severity and organ manifestations characterized by disease flares and remissions.*

Epidemiologic Data

Recent population-based studies in the United States have reported an increased incidence of SLE during the past few decades. Incidence is 9 per 100,000 persons, and prevalence is up to 128 per 100,000 persons; in some nonwhite ethnic groups, the prevalence has been reported to be higher. SLE is more common in girls and women than boys and men, with a female to male ratio ranging from 9:1 to 15:1. SLE is often seen in women of childbearing age; more than one-half of female patients with SLE have disease onset between age 16 years and their mid-40s. In postmenopausal women, the female to male ratio is closer to 2:1. The prevalence of SLE is higher among black, Native American, and Hispanic girls and women. Black girls and women tend to have a younger age of onset and a higher prevalence of renal complications in SLE.

Etiologic Factors

The cause of SLE is unknown, but multiple contributors to the pathogenesis have been identified. They include genetic, hormonal, immunologic, and environmental influences, such as UV light and viruses.

Genetics

Twin and family studies have shown that a genetic component contributes to SLE onset. Monozygotic twins have a higher concordance rate (>25%) than dizygotic twins. Large-scale genome-wide association studies have identified about 50 gene loci with multiple polymorphisms, including class II HLA genes, complement genes, and immunoglobulin (Ig) receptor genes that increase the risk of susceptibility to SLE.

Pathogenesis

The pathogenesis of SLE is characterized by a loss of tolerance to both self-antigens and autoantibody production. Immune complexes form that bind complement, release inflammatory mediators, and deposit in tissues, leading to injury. Innate immunity is activated by the circulating immune complexes through Toll-like receptors 7 and 9 and results in type I interferon-α production. This result leads to release of downstream proinflammatory cytokines such as tumor necrosis factor α, which is increased in specific SLE manifestations such as lupus nephritis. In addition, T and B cells have abnormalities, with a decrease in cytotoxic T cells and suppressor T-cell function and an increase in helper T cells and in B-cell hyperactivity, resulting in polyclonal activation and autoantibody production.

Clinical Manifestations

Mucocutaneous Signs

Lupus rashes have 4 common types: acute cutaneous, subacute cutaneous lupus erythematosus (SCLE), discoid, and lupus profundus. The acute cutaneous rash is characterized as an erythematous elevated or flat malar rash (butterfly rash) that spares the nasolabial folds and is exacerbated by sunlight (ie, is photosensitive). The SCLE rash is characterized by annular, erythematous rings with serpiginous borders and central hypopigmentation on sun-exposed areas, such as the arms, shoulders, neck, and trunk. SCLE rash is associated with anti–SS-A (Ro) and anti–SS-B (La) antibodies; it can occur in the absence of SLE manifestations. Discoid lupus is manifested by chronic, erythematous papular or plaquelike lesions involving the face, scalp, and extremities, and it may occur without SLE manifestations. Follicular plugging occurs with central atrophy, leading to scarring. Lupus profundus is an inflammatory panniculitis of the subcutaneous fat layer that variably appears as painful nodules on the extremities or trunk, or both.

Alopecia of varying degrees is a common feature of SLE. Hair loss may be diffuse or patchy and, similar to the malar rash, associated with SLE flares. Hair may regrow during disease remissions. In addition, hair loss may be an adverse effect of cytotoxic drugs, such as methotrexate or cyclophosphamide.

Oral ulcers are another common mucocutaneous characteristic of active SLE. They usually are painless and develop on the hard palate, buccal mucosa, or tongue. Ulcers also can occur on the lower nasal septum during active SLE.

Articular Outcomes

Polyarthralgia and inflammatory arthritis, are the most common presenting characteristic of SLE and affect up to 90% of patients. Unlike rheumatoid arthritis, SLE-related arthritis is classically nondeforming and nonerosive. The arthritis is symmetrical and typically involves the small joints of the hands, the wrists, and sometimes the knees. A subset of a deforming arthritis called *Jaccoud arthropathy* may occur in up to one-third of patients and is manifested by tendon inflammation and a nonerosive arthritis with joint subluxations and hand and finger contractures.

KEY FACTS

- ✓ SLE has onset during childbearing years and is more prevalent among nonwhite women
- ✓ Alopecia—a common mucocutaneous feature of SLE
- ✓ Ulcers can occur in the mouth and, less often, on the nasal septum in active SLE
- ✓ The most common presenting feature of SLE—polyarthralgia or inflammatory arthritis, or both (90% of cases)

Avascular necrosis of the bone may occur in SLE. The clinical presentation is acute joint pain and physical disability. The femoral head and tibial plateau are most commonly affected. Plain radiographs of the joint are often insensitive, but radionuclide bone scan or magnetic resonance imaging is useful in detecting avascular necrosis. Conservative therapy with avoidance of excessive weight-bearing activity is usually recommended, but joint replacement may be necessary.

Cardiovascular Effects

Cardiac involvement in SLE is manifested as pericarditis, myocarditis, endocarditis, accelerated coronary atherosclerosis, and rarely coronary vasculitis. The most common cardiac manifestation is pericarditis. It is characterized by chest pain and a pericardial rub, although clinically it may be silent. Nonbacterial vegetations on native valves can range from tiny lesions to large verrucous vegetations and can lead to valvular dysfunction, embolization, or infective endocarditis. Although rare, myocarditis should be suspected in a patient with SLE who has unexplained arrhythmias or cardiomegaly. An association between SLE and premature coronary artery disease has been established and can occur in inactive lupus as a late complication. Women with SLE in their mid-30s to mid-40s have a 50-fold increased risk of premature coronary atherosclerosis and myocardial infarction compared with age-matched women without SLE. In addition to the traditional cardiovascular risk factors, SLE carries an independent cardiovascular risk factor, possibly related to the immune-mediated vascular inflammation.

Pulmonary Signs

Pulmonary involvement may be manifested by any of the following conditions: pleurisy, pleural effusions, acute pneumonitis, pulmonary hypertension, pulmonary embolism, diffuse alveolar hemorrhage, and diaphragmatic dysfunction (ie, shrinking lung syndrome). Pleural manifestations are the most common pulmonary feature of SLE. Patients may give a clinical history of pleuritic chest pain without accompanying chest radiograph abnormalities. When detected, pleural effusions are often small and bilateral, but they can be massive. Lupus effusions are characteristically exudative with normal glucose concentration, in contrast to the effusions seen in rheumatoid arthritis, in which the glucose concentration is low. Diffuse alveolar hemorrhage is a serious but uncommon manifestation in SLE. It presents with cough and hemoptysis and is associated with a poor prognosis. Shrinking lung syndrome is rare and poorly understood, but the syndrome is thought to be secondary to abnormal respiratory muscles or diaphragmatic dysfunction and weakness.

Renal Factors

Renal involvement in SLE may occur in approximately 50% to 75% of patients. Nonwhite women with SLE are more often affected. The pathophysiologic process is primarily that of an immune complex–mediated glomerular disease related to the formation of anti–double-stranded DNA antibodies against nucleosomes that aggregate or directly bind to glomerular basement proteins. Elevated levels of anti–double-stranded DNA antibodies and low levels of complement (C3 and C4) may indicate active renal disease. The International Society of Nephrology and the Renal Pathology Society have classified lupus nephritis according to renal biopsy findings: minimal mesangial (class I), mesangial proliferative (class II), focal (class III), diffuse (class IV), membranous (class V), and advanced sclerosing (class VI). In addition, tubulointerstitial disease can coexist with glomerular disease and is seen with an elevated creatinine level, hypertension, and a progressive course. Thrombotic microangiopathy manifested by glomerular and vascular thrombi often may occur, with positive results for anticardiolipin antibodies and lupus anticoagulant. A less common occurrence is renal vein thrombosis with nephrotic syndrome.

Renal involvement may occur in asymptomatic patients; hence, routine monitoring of blood pressure, creatinine, and urinalysis is recommended twice a year or more frequently if urinary abnormalities are present. Renal involvement is manifested by proteinuria of greater than 0.5 g/24 hours or the presence of casts (eg, red blood cell, heme, granular, tubular, mixed). Additionally, signs of active renal disease are an elevated creatinine level and the presence of hematuria (>5 red blood cells per high-power field) or pyuria (>5 white blood cells per high-power field), or both, in the absence of infection. A strong predictor of lupus nephritis is an elevated level of anti–double-stranded DNA antibodies.

Renal biopsy results have both prognostic and therapeutic implications. Patients with high activity indices on biopsy, such as active inflammation, proliferation, necrosis, and crescent formation, are considered for aggressive therapy. Patients with high chronicity indices, such as tubular atrophy, interstitial fibrosis, scarring, and glomerulosclerosis, are less likely to respond to aggressive therapy. Chronic lesions are associated with decreased renal and patient survival.

Active focal or diffuse glomerulonephritis (class III and class IV) and membranous glomerulonephritis with nephrotic-range proteinuria (class V) are treated with induction therapy consisting of pulsed high-dose corticosteroid therapy, then oral corticosteroid therapy with taper and cyclophosphamide (intravenous route preferred to oral because of fewer complications). Mycophenolate mofetil has shown efficacy equivalent to cyclophosphamide with fewer adverse effects, and it is an option for induction and maintenance therapy in lupus nephritis. Rituximab, a chimeric monoclonal antibody against CD20 antigen and a B-cell–depleting agent, has gained increased use for induction therapy in refractory proliferative lupus nephritis. However, recent trials did not report increased efficacy compared with placebo in achievement of primary outcomes. Tacrolimus has gained increased use as a third-line agent for induction therapy in certain patient populations (for example, patients of Chinese ethnicity who have severe lupus nephritis or patients with resistant nephritis, for whom it would be an add-on therapy). After induction therapy, mycophenolate mofetil or azathioprine is generally used to maintain renal remission; azathioprine is preferred for women with childbearing potential. In approximately 10% to 30% of patients with lupus nephritis, end-stage renal disease develops within 15 years of the diagnosis, despite aggressive treatment.

KEY FACTS

✓ Wide range of cardiovascular manifestations in SLE—pericarditis (most common), valvular abnormalities, myocarditis, premature coronary atherosclerosis, myocardial infarction, coronary vasculitis

✓ The most common pulmonary feature of SLE—pleural manifestations

✓ The kidneys are involved in 50% to 75% of patients with SLE

✓ Treatment of classes III to V renal involvement in SLE—induction therapy with corticosteroids, cyclophosphamide, or mycophenolate mofetil; maintenance therapy with mycophenolate mofetil or with azathioprine for women of childbearing age

Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers should be used for patients with nephrotic-range proteinuria or chronic proteinuria, even without evidence of active renal disease. These agents have been shown to reduce proteinuria and have renoprotective effects. Statin therapy to control a high cholesterol level is advised. Aggressive blood pressure control is paramount to improving renal survival.

Neuropsychiatric Effects

The diagnosis of neuropsychiatric SLE (NPSLE) is controversial because of the difficulty in drawing clear associations between heterogeneous neurologic manifestations and active lupus disease. Additionally, numerous metabolic, infectious, or medication-induced mimickers need to be excluded before the NPSLE diagnosis is made. The SLE wide spectrum of manifestations is broadly categorized as central nervous system (CNS) or peripheral nervous system abnormalities by the American College of Rheumatology. Among the CNS manifestations are aseptic meningitis, seizure disorder, strokes, demyelinating disease, headache (severe headaches refractory to narcotics), movement disorders such as chorea, myelopathy, acute confusion, anxiety disorder, mood disorder, cognitive dysfunction, and psychosis. Among the peripheral manifestations are polyneuropathy, plexopathy, cranial neuropathy, myasthenia gravis, mononeuropathy, autonomic neuropathy, and Guillain-Barré syndrome.

The pathogenesis of CNS lupus is not well understood. On autopsy, common findings are microinfarcts, small-vessel wall thickening, and nerve cell loss. Thrombotic occlusion of larger vessels and vasculitis (inflammatory infiltrate with fibrinoid necrosis) are seen less commonly.

The diagnosis of NPSLE is usually a clinical one. Cerebrospinal fluid (CSF) analysis is important and may show increased CSF protein IgG, pleocytosis, increased protein, decreased glucose, antineuronal antibodies, and antiribosomal P antibodies. Results of electroencephalography may be abnormal but nonspecific. Computed tomography (CT) brain studies may show areas of infarctions, hemorrhage, or cortical atrophy. Magnetic resonance imaging studies are superior to CT scans and show areas of increased signal intensity in the periventricular white matter, similar to those found in multiple sclerosis.

Gastrointestinal Tract Outcomes

Gastrointestinal tract involvement in SLE ranges from nausea to esophageal reflux, mesenteric vasculitis, liver disease (eg, lupoid hepatitis), and pancreatitis. A gastrointestinal tract syndrome that occurs during SLE disease exacerbations is manifested by acute abdominal pain, nausea, and anorexia from peritoneal inflammation. Ascites, including massive ascites, may also be present, but infection or malignancy, or both, must be ruled out with paracentesis. Chronic painless ascites may occur in a subset of patients without other manifestations of active lupus.

Hematologic Signs

Hematologic abnormalities are frequent manifestations of SLE. Anemia of chronic disease is often seen, but hemolytic anemia (Coombs test positive) is less common. Leukopenia ranges from 2,500 to 4,000 leukocytes/mm^3 but usually does not predispose to infections; it may be associated with active SLE secondary to antilymphocyte antibodies. Thrombocytopenia is also common. Idiopathic thrombocytopenic purpura with platelet antibodies can precede a diagnosis of SLE. Patients may have mild petechiae or easy bruising. Antiphospholipid antibody syndrome (APS) should be suspected in patients with chronic, refractory thrombocytopenia.

Diagnosis

The diagnosis of SLE is challenging to make because many of its features are nonspecific: Patients may present with symptoms that mimic other inflammatory disorders, such as infection and malignancy. In general, the diagnosis is based on various clinical manifestations and laboratory findings. Classification criteria developed by expert consensus, such as the 1997 American College of Rheumatology criteria (4 of 11 criteria must be met) or the 2012 Systemic Lupus International Collaborating Clinics criteria (4 of 17 criteria must be met), aid researchers in categorizing patient concerns. However, the criteria may be problematic in the confirmation of a diagnosis because of the heterogeneity of disease manifestations. Classic clinical characteristics of patients with SLE are listed in Box 80.1, adapted from the 1997 American College of Rheumatology criteria.

The clinical importance of autoantibodies in SLE depends on the type and level of the autoantibodies. Although almost all patients with SLE (>95%) have positive results of antinuclear antibody (ANA) tests, a positive result is not specific for SLE. Asymptomatic persons without SLE may have a low-titer ANA (eg, 1:40) result of no clinical importance. Anti–double-stranded DNA levels are specific for SLE; the levels fluctuate, and high levels are used as a marker for disease activity, especially in lupus nephritis. Levels of other autoantibodies (eg, ribonucleoprotein [RNP], Smith [Sm], ANA) do not correlate with SLE disease activity. The anti-Sm antibody is highly specific for SLE. ANA patterns are outlined in Table 80.1. Other autoantibodies and disease associations are listed in Table 80.2.

Box 80.1 • Classification Criteria for Diagnosis of Systemic Lupus Erythematosus

Malar rash
Discoid lupus
Photosensitivity
Oral ulcers
Nonerosive arthritis of 2 or more peripheral joints
Serositis: pleuritis or pericarditis
Renal disorder: proteinuria (protein >0.5 g/d) or cellular casts
Neurologic disorder: seizures or psychosis
Hematologic disorder: hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia
Immunologic disorder: anti–double-stranded DNA, anti-Smith, antiphospholipid antibodies
Positive antinuclear antibody test in the absence of offending drugs

Data from American College of Rheumatology. 1997 Update of the 1982 American College of Rheumatology revised criteria for classification of systemic lupus erythematosus [Internet]. Atlanta (GA): American College of Rheumatology; c1997 [cited 2019 Apr 10]. Available from: http://www.ncbi.nlm.nih.gov/pubmedhealth/ PMH0041704/.

KEY FACTS

- ✓ A syndrome of acute abdominal pain, nausea, and anorexia from peritoneal inflammation can occur during SLE exacerbations
- ✓ Common hematologic manifestations of SLE—anemia of chronic disease, leukopenia, and thrombocytopenia
- ✓ Anti–double-stranded DNA—levels correlate with SLE disease activity; levels of other autoantibodies do not
- ✓ The anti-Sm antibody is highly specific for SLE
- ✓ Autoantibodies—prevalent in SLE and other connective tissue diseases but must be interpreted cautiously within the clinical context

Table 80.1 • Antinuclear Antibody Patterns

Fluorescent Pattern	Antigen	Disease Association
Rim, peripheral, shaggy	nDNA	SLE
Homogeneous	DNP	SLE, DIL, others
Speckled	ENA	MCTD, SLE, Sjögren syndrome
Nucleolar	RNA	Scleroderma

Abbreviations: DIL, drug-induced lupus; DNP, deoxyribonucleoprotein; ENA, extractable nuclear antigen; MCTD, mixed connective tissue disease; nDNA, native DNA; SLE, systemic lupus erythematosus.

Treatment

The SLE disease course is characterized by periods of increased disease activity (flares), persistent symptoms, remission, and cumulative damage of involved organs. Treatment should match the disease activity and the severity of organ system involvement. Frequent monitoring of disease activity (eg, anti–double-stranded DNA, C3, C4, erythrocyte sedimentation rate [ESR], proteinuria) allows for rapid recognition and treatment of SLE flares. Table 80.3 provides guidelines for treatment, and Table 80.4 outlines the complications of treatment.

Table 80.2 • Autoantibodies in Rheumatic Diseases

Antibody	Disease Association
Anti–double-stranded DNA	SLE, 50%-70%
Anti-Smith	SLE, 30%
Anti-U1-RNP (ribonucleoprotein)	MCTD, 100% at high titer; SLE, 30%; scleroderma
Anti–SS-A (Ro)	Sjögren syndrome, 70%; SLE, 35%; scleroderma + MCTD; neonatal lupus
Anti–SS-B (La)	Sjögren syndrome, 60%; SLE, 15%; neonatal lupus
Antihistone	Drug-induced SLE, 95%; SLE, 60%; RA, 20%
Anti–Scl-70 (antitopoisomerase I)	Scleroderma, 25%
Anticentromere	CREST, 70%-90%; scleroderma, 10%-15%
Anti-PM1 (polymyositis)	PM, 50%
Anti-Jo1 (antisynthetase)	Antisynthetase syndrome (dermatomyositis, PM, interstitial lung disease, fever, inflammatory arthritis, Raynaud phenomenon), 30%

Abbreviations: CREST, syndrome of *c*alcinosis cutis, *R*aynaud phenomenon, *e*sophageal dysmotility, *s*clerodactyly, and *t*elangiectasia; MCTD, mixed connective tissue disease; PM, polymyositis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Table 80.3 • Commonly Used Therapies for Manifestations of Systemic Lupus Erythematosus

Manifestation	Treatment
Arthritis, fever, mild systemic symptoms	ASA, NSAID, low-dose corticosteroids
Photosensitivity, rash	Avoidance of sun, use of sunscreens with SPF of 50 or higher, topical corticosteroids and/or topical tacrolimus, oral hydroxychloroquine, oral chloroquine
Rash, arthritis	Hydroxychloroquine, methotrexate, leflunomide, azathioprine (Imuran), belimumab
Notable thrombocytopenia, hemolytic anemia	Corticosteroids, IVIG
Renal disease, CNS disease, pericarditis, other important organ involvement	Corticosteroids, cyclophosphamide, cyclosporine
Rapidly deteriorating renal function	Cyclophosphamide, mycophenolate mofetil, azathioprine

Abbreviations: ASA, acetylsalicylic acid; CNS, central nervous system; IVIG, intravenous immunoglobulin; NSAID, nonsteroidal anti-inflammatory drug; SPF, sun protection factor.

Hydroxychloroquine has been regarded as an essential medication for long-term treatment of SLE because of its low adverse effect profile, its benefits in reducing organ damage and thrombosis, and its association with increased patient survival. Belimumab, a monoclonal antibody that inhibits the B-lymphocyte stimulator, the soluble B-cell–activating factor, has been approved as a biologic agent available for treatment of the cutaneous and articular manifestations of SLE nonresponsive to conventional therapy. Studies are under way to expand the indications for its use in other SLE manifestations. Rituximab has been gaining use as an off-label alternative for major SLE manifestations, such as in NPSLE and proliferative nephritis, but recent trials have not shown statistically significant benefits.

Pregnancy and SLE

Women with SLE who become pregnant have a high prevalence of pregnancy-related complications, such as preterm premature rupture of membranes, preeclampsia, thrombosis, and spontaneous abortion. Moreover, patients with SLE typically have increased disease activity during pregnancy, possibly related to fluctuating hormone levels. Predictors of SLE flares during pregnancy are the presence of anti–double-stranded DNA or antiphospholipid antibodies, or both; active renal disease; and low complement levels before conception. SLE flares should be treated with corticosteroids; however, the risk of hypertension and gestational diabetes is increased with prolonged

Table 80.4 • Complications of Treatment of Systemic Lupus Erythematosus

Treatment	Complication
Ibuprofen	Aseptic meningitis (headache, fever, stiff neck, CSF pleocytosis)
NSAID	Decreased renal blood flow
ASA	Salicylate hepatitis (common), benign
Corticosteroids	Avascular necrosis, diabetes mellitus, hypertension, osteoporosis, dyslipidemia, obesity
Hydroxychloroquine	Retinal toxicity, skin hyperpigmentation
Methotrexate	Mucositis, hepatitis, nausea, loose stools, hair loss
Leflunomide	Elevated liver enzyme levels, cytopenias, diarrhea
Azathioprine	Nausea, cytopenias, pancreatitis
Immune globulin	Infusion reactions, headaches
Mycophenolate mofetil	Nausea, headaches, hypertension, cytopenias, increased risk of nonopportunistic and opportunistic infections, colitis
Cyclophosphamide	Hemorrhagic cystitis, alopecia, nonopportunistic and opportunistic infections, increased incidence of lymphomas (CNS), sterility (premature ovarian failure)
Cyclosporine	Hypertension, hirsutism, hyperkalemia, hypomagnesemia, renal failure
Belimumab	Nonopportunistic and opportunistic infections, infusion reactions, diarrhea

Abbreviations: ASA, acetylsalicylic acid; CNS, central nervous system; CSF, cerebrospinal fluid; NSAID, nonsteroidal anti-inflammatory drug.

corticosteroid use. Almost all of the immunosuppressants are contraindicated during pregnancy, with the exception of hydroxychloroquine and azathioprine.

Prognosis

The 10-year survival rate is about 90% in newly diagnosed SLE. Yet, despite improved management of SLE and its complications, patients still have a mortality risk 3 times higher than that of the general population. Deaths in early lupus (about 1 year after diagnosis) are attributed to active disease; deaths beyond 1 year are attributed to premature cardiovascular atherosclerosis and infection. Prognosis is worse for African Americans, persons of Hispanic ethnicity, and men. Progressive renal disease or CNS disease is associated with decreased survival. SLE also affects work productivity and contributes to increased health care costs, disability, and a poor quality of life. The major causes of death are active SLE disease, infection, and premature cardiovascular disease.

Drug-Induced Lupus

Many drugs have been implicated as causative in drug-induced lupus (DIL). The most common of these are listed in Box 80.2. Hydralazine, procainamide, and methyldopa have been classically associated with DIL. The pathogenesis is complex, but it is related in part to inhibition of DNA methylation and transformation of the drug to reactive metabolites. A DIL syndrome develops in 5% to 10% of patients taking hydralazine and in 15% to 25% of those taking procainamide. DIL may be underreported since many cases resolve after the offending drug has been removed from the treatment regimen.

Clinical Manifestations

In contrast to SLE, DIL has an almost equal sex distribution and is predominantly in the older population. More cases of

Box 80.2 • Implicated Agents in Drug-Induced Lupus

- Definite
  - Procainamide
  - Hydralazine
  - Isoniazid
  - Methyldopa
  - Penicillamine
  - Diltiazem
  - Quinidine
  - Minocycline
  - Anti-TNF drugs
  - Interferon alfa
- Probable
  - Phenytoin
  - Carbamazepine
  - Ethosuximide
  - Propylthiouracil
  - Sulfasalazine
  - Captopril
  - Lithium carbonate
  - Acebutolol
  - Terbinafine
- Possible
  - Penicillin
  - Tetracycline
  - Valproate
  - Statins
  - Gemfibrozil
  - Hydrochlorothiazide

Abbreviation: TNF, tumor necrosis factor.

DIL in older men are due to hydralazine and procainamide, probably because of increased use among this demographic group. Clinical manifestations of DIL include fever, malaise, rash, arthralgias, myalgias, and serositis. The rashes can manifest as purpura or erythematous papular lesions, although subacute cutaneous lupus, discoid lupus, and malar rashes may occur. Approximately 30% of patients have serositis, particularly with procainamide use. Pericarditis has been reported in approximately 20% of patients. Asymptomatic pleural effusions may be found on chest radiography. In contrast to SLE, CNS and renal manifestations are rare in DIL.

Laboratory Findings

Almost all patients with SLE or DIL have a positive ANA result. Anti–double-stranded DNA is found in a small percentage of cases, especially when anti–tumor necrosis factor and interferon alfa agents have been used. In contrast to SLE, serum total hemolytic complement, C3, and C4 values are usually normal in DIL. Antibodies such as anti-Sm, anti–SS-A, anti–SS-B, and anti-RNP are also unusual in DIL. The frequency of antihistone antibodies is high (>95% of cases), but these antibodies also occur in approximately 60% of SLE cases.

Diagnosis

The diagnosis of DIL is made through establishment of a timeline between onset of symptoms after initiation of drug use, which ranges from 3 weeks to 2 years, and rapid improvement or resolution after discontinuation of drug use, usually within 6 weeks. An ANA test should be obtained. To definitively diagnose DIL, some clinicians may treat patients with the same drug or a similar drug of the same class to determine whether signs and symptoms recur.

Treatment

Patients with DIL should discontinue the offending drug. Symptoms usually subside within several weeks, although the duration for complete resolution varies. Serologic abnormalities (eg, a positive ANA result) can persist for years after resolution of clinical symptoms. Treatment depends on the clinical manifestations and may include nonsteroidal anti-inflammatory drugs or low-dose corticosteroids for arthralgias, fever, and serositis symptoms.

Mixed Connective Tissue Disease

Mixed connective tissue disease (MCTD) is a distinct disease with features that overlap with SLE, systemic sclerosis, polymyositis, and inflammatory arthritis. It is serologically characterized with a positive ANA result and a high titer of anti-U1-RNP antibody. The female to male predominance is high (10:1). MCTD clinical manifestations are bilateral hand edema, Raynaud phenomenon, arthritis, and myositis. In some patients with MCTD, phenotype may eventually evolve to be characteristic of systemic sclerosis or SLE. Pulmonary arterial hypertension is associated with MCTD and typically results in a poor prognosis.

KEY FACTS

✓ Three drugs classically associated with DIL—hydralazine, procainamide, and methyldopa

✓ Antihistone antibodies—occur in more than 95% of cases of DIL and in about 60% of SLE cases

✓ To diagnose DIL, establish that symptoms (eg, fever, rash, arthritis, serositis) that began after the drug was started and rapidly improved after it was stopped

✓ Characteristic serologic findings in mixed connective tissue disease—ANAs and a high titer of anti-U1-ribonucleoprotein antibody

Undifferentiated Connective Tissue Disease

Patients with undifferentiated connective tissue disease have symptoms that do not fulfill the diagnostic criteria for a definite or specific connective tissue disease. Common symptoms include Raynaud phenomenon, arthralgias, sicca, fatigue, and polyarthralgia. The ANA result may be positive—usually of low to medium titer—but other autoantibodies are not present. Surveillance of these patients is required to determine whether progression to a distinct connective tissue disease occurs.

Antiphospholipid Antibody Syndrome

APS is an autoimmune clotting disorder characterized by recurrent venous and arterial thrombosis or pregnancy morbidities, or both. The syndrome is diagnosed with clinical and laboratory criteria. Definite APS is diagnosed when at least 1 clinical criterion and 1 laboratory criterion are met. The clinical and laboratory criteria are outlined in Table 80.5.

Many, but not all, patients with lupus anticoagulant also have increased IgG or IgM antiphospholipid antibody levels. These antibodies may be found in patients with no apparent disease in whom recurrent thrombosis develops; these patients have primary APS. Secondary APS occurs in the clinical setting of an underlying condition, such as SLE, infection, or malignancy. It also is common to see transiently elevated antiphospholipid antibody levels or lupus anticoagulant, or both, due to infection or an inflammatory state, or both. Hence, a confirmatory testing is needed 12 weeks later.

Table 80.5 • Criteria for Antiphospholipid Antibody Syndrome[a]

Clinical Criteria	Laboratory Criteria
Venous, arterial, or small-vessel thrombosis in any organ[b]	Medium to high levels of IgG and/or IgM antiphospholipid antibodies (>40 GPL or MPL) or above the 99th percentile on 2 occasions at least 12 weeks apart with ELISA
One or more fetal losses with normal fetal morphologic characteristics, unexplained, and after 10 weeks' gestation	IgG and/or IgM anti–β_2-glycoprotein-1 antibodies at a titer above the 99th percentile on 2 or more occasions at least 12 weeks apart with ELISA
One or more premature births at or before 34 weeks' gestation due to severe preeclampsia, eclampsia, or placental insufficiency	
Three or more recurrent fetal losses before 10 weeks' gestation	Lupus anticoagulant with dilute Russell viper venom time and aPTT, followed by a mixing study and confirmatory testing on 2 occasions 12 weeks apart

Abbreviations: aPTT, activated partial thromboplastin time; ELISA, enzyme-linked immunosorbent assay; GPL, IgG phospholipid unit; IgG, immunoglobulin G; IgM, immunoglobulin M; MPL, IgM phospholipid unit.

[a] These criteria represent a version of the revised 2006 Sapporo classification criteria.

[b] Superficial venous thrombosis does not satisfy this criterion.

Modified from Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006 Jan;4(2):295-306; used with permission.

Clinical Characteristics

Multiple organ systems may be affected to various degrees. Patients with recurrent venous thromboses most often have involvement of the deep and superficial veins of the leg. Patients with recurrent arterial thromboses may have strokes (secondary to valvular emboli) or transient ischemic attacks, as well as retinal, coronary, brachial, or mesenteric thromboses. Libman-Sacks endocarditis and other valvular abnormalities have been reported, such as thickening, stenosis, and vegetations in up to 50% of patients with APS. Various skin abnormalities have been observed, such as livedo reticularis, digital gangrene, nailfold infarcts, and leg ulcers.

The hallmark laboratory features of APS are persistent thrombocytopenia and prolongation of the activated partial thromboplastin time (aPTT). The failure of normal plasma to correct the aPTT distinguishes lupus anticoagulant and antiphospholipid antibody from clotting factor deficiencies. In addition, a Coombs-positive hemolytic anemia is a characteristic finding in APS.

Catastrophic APS refers to development of thrombosis in 3 or more organ systems with positive results for antiphospholipid antibodies or lupus anticoagulant, or both, in a short time, such as a week. Life-threatening organ ischemia often occurs in the CNS and pulmonary, renal, gastrointestinal tract, and cardiac systems. Patients may present with acute pulmonary hemorrhage, confusion, acute abdominal pain due to bowel infarction, and renal insufficiency requiring hemodialysis, depending on the extent of catastrophic APS and the organs involved. These patients are best treated in a critical care setting. Prognosis is poor, and treatment often involves multiple courses of plasma exchange, high-dose glucocorticoid therapy, and anticoagulation. Data on use of rituximab in refractory APS are limited, but rituximab use has been increasing.

Key Definition

Catastrophic antiphospholipid antibody syndrome: *thrombosis of 3 or more organ systems with positive results for antiphospholipid antibodies or lupus anticoagulant, or both, in a short period, such as 1 week.*

Treatment

The initial approach to APS treatment involves use of unfractionated heparin or low-molecular-weight heparin (LMWH) in combination with warfarin for 3 to 5 days until the warfarin reaches a therapeutic effect, with an increased international normalized ratio (INR) of 2 to 3. For most patients with definite APS and thrombosis, warfarin will need to be taken indefinitely. For pregnant women with definite APS, subcutaneous LMWH is used; warfarin is resumed in the postpartum period. For pregnant women with definite APS and a history of prior pregnancy morbidity, low-dose aspirin and LMWH are used in combination. Patients with either antiphospholipid antibodies or lupus anticoagulant should not receive estrogen-containing oral contraceptive pills, since these patients may be at higher risk for thrombosis. For patients who have recurrent thrombosis despite warfarin treatment and an INR of 2 to 3, additional intensive therapy is suggested, such as an increase in target INR range to 3 to 4 and the addition of LMWH and low-dose aspirin therapy. Monitoring the INR of patients with APS may be problematic because of potential relationship to the presence of antiprothrombin antibodies, which may falsely prolong the prothrombin time even without warfarin therapy or lupus anticoagulant, or both, increasing the INR. Monitoring factor Xa levels may be a solution.

Raynaud Phenomenon

Raynaud phenomenon refers to reversible digital vasospasm characterized by classic triphasic color changes (pallor, cyanosis, and reactive hyperemia followed by erythema). It often is accompanied by pain and numbness in the fingers, hands, toes, or feet, or a combination. Constriction of the digital vessels leads to pallor, cyanosis results from blood stasis marked by deoxygenation, and reactive hyperemia is due to increased blood flow.

Raynaud phenomenon has primary and secondary forms. Primary Raynaud phenomenon is often mild and is characterized by symmetrical digit involvement in young women. This group of patients may be at risk for a connective tissue disorder if results of an ANA test are positive. Cold or emotional stress is a common precipitating agent. Primary Raynaud phenomenon is a clinical diagnosis, although investigation should be made into secondary causes with such tests as a complete blood cell count, ANA, ESR, C-reactive protein, creatinine, urinalysis, and serum protein electrophoresis.

Key Definition

Raynaud phenomenon: *reversible digital vasospasm characterized by classic, triphasic color changes (pallor, cyanosis, and reactive hyperemia followed by erythema).*

Secondary Raynaud phenomenon is associated with an underlying disorder, such as a connective tissue disease (eg, systemic sclerosis, MCTD). Nailfold capillary microscopy reveals tortuous, enlarged dilated capillary loops in systemic sclerosis, MCTD, and dermatomyositis. These patients may have nail pitting, periungual telangiectasias, scarring, loss of digital pulp, and gangrenous changes. Other causes of secondary Raynaud phenomenon are listed in Box 80.3 and include vasoconstriction effects from drugs, occlusive vascular disorders, and occupational hazards.

Treatment involves conservative management, such as the wearing of mittens or gloves to keep the core body temperature elevated and the avoidance of precipitating factors, such as vasoconstricting drugs. Smoking cessation should be emphasized. Vasodilators, such as calcium channel blockers, are the mainstays of treatment. Commonly used calcium blockers are nifedipine, amlodipine, and diltiazem. Other, less commonly used agents are 2% nitrate paste, α-blockers, sildenafil, phosphodiesterase-5 inhibitors, and intravenous or oral prostacyclin analogues. Surgical treatment is rarely used but is often necessary for the patients who have severe Raynaud phenomenon with digital ischemia accompanied by tissue loss and pain. For these patients, a stellate ganglion block, digital nerve block, or surgical digital sympathectomy is done.

Box 80.3 • Causes of Secondary Raynaud Phenomenon

- Connective tissue diseases
  - Scleroderma
  - Mixed connective tissue disease
  - Sjögren syndrome
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Polymyositis/dermatomyositis
  - Antiphospholipid antibody syndrome
  - Cryoglobulinemia
- Drugs
  - Bleomycin
  - Vinblastine
  - Bromocriptine
  - Cyclosporine
  - β-Blockers
  - Antimigraine agents (eg, sumatriptan)
  - Toxins (eg, cocaine)
- Vascular occlusive disorders
  - Increased blood viscosity (paraproteinemia)
  - Thoracic outlet obstruction
  - Atherosclerosis
  - Vasculitis
  - Microemboli
  - Thromboangiitis obliterans (Buerger disease)
- Occupational hazards
  - Jackhammer use
  - Cold injury
  - Polyvinyl chloride exposure
- Miscellaneous
  - Cold agglutinins
  - Hepatitis infection

Systemic Sclerosis (Scleroderma)

Systemic sclerosis (SSc) (scleroderma) is divided into several categories: diffuse systemic sclerosis (diffuse scleroderma); limited scleroderma, which includes CREST (*c*alcinosis cutis, *R*aynaud phenomenon, *e*sophageal dysmotility, *s*clerodactyly, *t*elangiectasias); and localized scleroderma, such as morphea and linear scleroderma manifested by indurated plaques over extremities and torso. SSc sine scleroderma is rare and is characterized by internal organ involvement without classic skin manifestations. For the diagnosis of SSc, the major criterion or 2 or more minor criteria need to be present. The major criterion is symmetrical induration of the skin of the fingers and the skin proximal to metacarpophalangeal or metatarsophalangeal joints. The minor criteria are sclerodactyly, digital pitting scars in or loss of substance from the finger pad, and bibasilar pulmonary fibrosis. The pathologic hallmarks of scleroderma are an obliterative noninflammatory vasculopathy, proliferation of fibroblasts, and excessive accumulation of collagen in the skin and other organs, leading to fibrosis.

KEY FACTS

- ✓ For a diagnosis of definite APS, at least 1 clinical criterion and 1 laboratory criterion must be met
- ✓ Hallmark laboratory features of APS—persistent thrombocytopenia and prolongation of activated partial thromboplastin time
- ✓ If normal plasma does not correct the activated partial thromboplastin time, the problem is lupus anticoagulant and antiphospholipid antibody, not clotting factor deficiencies
- ✓ The 3 categories of SSc (scleroderma)—diffuse systemic sclerosis (diffuse scleroderma), limited cutaneous scleroderma (including CREST), and localized scleroderma

Clinical Manifestations

Cutaneous Signs

Three skin stages have been described in SSc. In stage 1, marked edema of hands or fingers occurs because of inflammation with a loss of skin folds. Decreased sweat and oil production leads to dry, cracked skin refractory to standard moisturizing agents. Diffuse pruritus may be present because of elaboration of histamine and bradykinin. Stage 2 SSc is characterized by progressive skin fibrosis resulting in hardened skin at fingertips and progressing proximally; the face, chest, abdomen, and upper thighs may be involved in addition to the distal extremities. In stage 3 (late stage), skin softening develops from atrophy with some hair regrowth. Patients with rapidly progressive acral and trunk skin thickening are at risk for early visceral abnormalities, such as scleroderma renal crisis.

Raynaud Phenomenon

Raynaud phenomenon occurs in more than 95% of persons with scleroderma. Onset may be years before cutaneous findings of scleroderma are evident. In some patients, Raynaud phenomenon may occur simultaneously with skin changes. Its lack should trigger an investigation into the other causes of skin induration (Box 80.4). Patients with SSc have abnormal nailfold capillaries that can be visualized by an ophthalmoscope; these are manifested by prominent vasculature with dropout. Because of intimal fibrosis and structural abnormalities of the microvasculature, digital pitting, ulcers, and other digital ischemic changes may develop.

Box 80.4 • Scleroderma Spectrum Disorders

Morphea
Eosinophilic fasciitis
Scleredema
Scleromyxedema
Nephrogenic systemic fibrosis

Articular Factors

A nondeforming, symmetrical inflammatory polyarthritis similar to rheumatoid arthritis may precede cutaneous manifestations, with involvement of the proximal interphalangeal joints, metacarpophalangeal joints, and wrists. Use of immunosuppressants, such as methotrexate or azathioprine, for treatment of the arthritis may be helpful. However, with progressive skin thickening and fibrosis, fixed flexion contractures may occur at multiple proximal interphalangeal joints, leading to structural deformities. Tendon friction rubs may be heard at the wrists, elbows, or ankles, or a combination.

Pulmonary Factors

Pulmonary involvement in the form of interstitial lung disease (ILD) or pulmonary arterial hypertension (PAH), or both, is a common cause of morbidity and death in SSc. Characterized by a basilar distribution, ILD may occur in approximately 70% to 80% of patients. It is the most common pulmonary abnormality in SSc, especially for patients with diffuse SSc. Pulmonary function testing with spirometry should be obtained to screen for ILD. A reduction in the diffusing capacity of the lung for carbon monoxide (DLCO) is a sensitive means for detection of early ILD. A reduced DLCO should be investigated with high-resolution CT to determine whether active alveolitis is present (ie, ground-glass opacities and reticular densities).

The histologic pattern of most patients is nonspecific interstitial pneumonia, which is often fibrotic. Patients who have active alveolitis detected with bronchopulmonary lavage with increased neutrophil count; high-resolution CT showing ground-glass opacities without honeycombing; or lung biopsy may respond to low-dose prednisone and cyclophosphamide therapy. Treatment of ILD is oral or intravenous (preferred route) cyclophosphamide for 6 to 12 months. This treatment may result in mild to moderate improvement of pulmonary function parameters and stabilize the ILD progression, although therapeutic effects may not be sustained after 1 to 2 years. Mycophenolate mofetil has been gaining use as an alternative to cyclophosphamide because it has relatively less toxicity, although larger randomized controlled trials are needed to validate that it has efficacy similar to cyclophosphamide. Azathioprine is an alternative agent but is less effective than cyclophosphamide.

KEY FACTS

- ✓ In SSc, rapidly progressive acral and trunk skin thickening indicates increased risk of early visceral abnormalities
- ✓ Common cause of morbidity and death in SSc—pulmonary involvement (interstitial lung disease or pulmonary arterial hypertension, or both)
- ✓ Treatment of interstitial lung disease in SSc with oral or intravenous (preferred) cyclophosphamide may stabilize progression
- ✓ Pulmonary arterial hypertension in SSc is treated with phosphodiesterase-5 inhibitors, prostacyclin analogues, and endothelin receptor antagonists

Patients with PAH may have an isolated decrease in Dlco with normal lung volumes. PAH is more common in patients with the CREST, or limited scleroderma, variant. Although echocardiography is helpful for making the diagnosis of PAH, right-sided heart catheterization should be performed to confirm the diagnosis and to obtain accurate measurements of pulmonary artery and capillary wedge pressures. PAH is associated with a high mortality rate. Treatment options involve phosphodiesterase-5 inhibitors such as sildenafil; prostacyclin analogues, such as iloprost, epoprostenol, and treprostinil; and endothelin receptor antagonists, such as bosentan and ambrisentan. These agents have improved patient symptoms and delayed PAH progression.

Cardiac Characteristics

Cardiac abnormalities occur in up to 70% of patients with SSc. Conduction defects and arrhythmias are the most common abnormalities because of fibrosis of conduction pathways; the most common abnormality is premature ventricular contractions. Other manifestations include pericardial abnormalities such as pericardial effusions and fibrinous pericarditis, diastolic dysfunction, and a dilated cardiomyopathy. Postmortem examination of the myocardium reveals inflammatory infiltrates in muscle cells and fibrosis with contraction band necrosis.

Gastrointestinal Tract Manifestations

Esophageal dysfunction is the most frequent gastrointestinal tract abnormality. It occurs in more than 90% of patients with SSc and may be asymptomatic. Lower esophageal sphincter incompetence with decreased sphincter tone results in dyspepsia; long-term injury from acid reflux may produce Barrett esophagus, esophageal strictures, or ulcers. Proton pump inhibitors reduce gastric acid production. Dysphagia can occur from involvement of the smooth muscle of the distal two-thirds of the esophagus. Esophageal dysmotility may respond to therapy with metoclopramide, cisapride, octreotide, or erythromycin. Telangiectasias of the gastric mucosa may result in chronic blood loss, leading to iron deficiency anemia; gastric antral vascular ectasias may give the appearance of a so-called watermelon stomach on endoscopy. Vascular ectasias may be treated with laser intervention. Small-bowel hypomotility may be associated with pseudo-obstruction, bowel dilatation, bacterial overgrowth, and malabsorption. Treatment with rotating antibiotic therapy may be helpful; promotility agents are less effective. Colonic dysmotility also occurs, and wide-mouthed diverticula may be found; intestinal pneumatosis may result from perforation of small- or large-bowel diverticula. The incidence of primary biliary cirrhosis is increased, especially in limited scleroderma or CREST.

Renal Effects

Scleroderma renal crisis (SRC) is an uncommon but organ-threatening manifestation of SSc. It is typically associated with progressive diffuse skin involvement, use of corticosteroids at doses greater than 15 mg per day, and other serious immunosuppression several weeks before onset. SRC develops in approximately 10% of persons with SSc. It is characterized by intimal proliferation and thrombosis of renal afferent arterioles and a high-renin state. Fulminant hypertension, renal failure that leads to hemodialysis, and death may occur if SSc is not treated aggressively. Patients typically present with newly diagnosed hypertension (although some patients may be normotensive), proteinuria, hematuria, microangiopathic hemolytic anemia, thrombocytopenia, and "onion skinning" that is manifested by endothelial proliferation, medial hypertrophy, and adventitial fibrosis on renal biopsy. SRC can be easily confused with thrombotic thrombocytopenic purpura. Clarification of the diagnosis is imperative so that appropriate treatment is not delayed, since plasmapheresis is contraindicated with use of ACE inhibitors. Aggressive early antihypertensive therapy with ACE inhibitors can extend life expectancy in SRC. Prognosis was poor and mortality rate was high before the advent of ACE inhibitors. These agents should be continued even if the patient progresses to dialysis because of the potential for recovery of kidney function.

Laboratory Findings

ANAs are found in 95% or more of patients with scleroderma. Patients with SSc may have positive results for antitopoisomerase I (anti–Scl-70) antibody. The presence of anti–Scl-70 antibody is associated with an increased risk of progressive skin and lung fibrosis. The presence of anti-RNA polymerase III antibody is associated with an increased risk of SRC.

Treatment

Treatment of SSc depends on the organs involved, as discussed in the preceding sections. Aggressive nutritional support, including hyperalimentation, may be required for extensive gastrointestinal tract disease.

Table 80.6 • Clinical Findings in Limited and Diffuse Scleroderma

	Cutaneous Disease	
Clinical Finding	**Limited**	**Diffuse**
Raynaud phenomenon	Precedes other symptoms by years	Onset may be simultaneous or associated with other symptoms within 1 year
Nailfold capillaries	Dilated	Dilated with dropout
Skin changes	Distal to elbow	Proximal to elbow with involvement of trunk
Telangiectasia, digital ulcers, calcinosis	Frequent	Rare early, but frequent later in the course
Joint and tendon involvement	Uncommon	Frequent (tendon rubs)
Visceral disease	Pulmonary hypertension	Renal, intestinal, and cardiac disease; pulmonary interstitial fibrosis
Autoantibodies	Anticentromere (70%-90%)	Antitopoisomerase I (anti–Scl-70) (25%)
10-year survival	>70%	≤70%

Limited Scleroderma or CREST Syndrome

In CREST syndrome, skin involvement progresses slowly and is limited to the face, neck, and distal extremities. Internal organ involvement occurs but is delayed. Lung involvement occurs in 70% of patients. PAH is more common in CREST than in diffuse scleroderma. Patients with the CREST variant may have a positive result for anticentromere antibodies.

The clinical manifestations of limited and systemic scleroderma are described in Table 80.6.

Sjögren Syndrome

Sjögren syndrome (SS) is an autoimmune disorder characterized by decreased lacrimal and salivary gland function due to lymphocytic infiltration of the glands. The syndrome manifests with dry eyes (keratoconjuctivitis sicca) and dry mouth (xerostomia). It affects less than 1% of the US population and is more common in women than men (9:1 ratio). Onset usually occurs in the 40s to 50s. There are 2 types of SS: primary and secondary. In secondary SS, an underlying connective tissue disease is present, such as rheumatoid arthritis, MCTD, or SLE.

Key Definition

Sjögren syndrome: *an autoimmune disorder characterized by decreased lacrimal and salivary gland function due to lymphocytic infiltration of the glands; manifests with progressive dry eyes (keratoconjuctivitis sicca) and dry mouth (xerostomia).*

Clinical Manifestations

The symptoms and clinical features of SS can be categorized broadly into glandular and extraglandular manifestations. The glandular clinical features are the classic sicca symptoms manifested by a sensation of grittiness in the eyes and a dry mouth necessitating frequent sips of fluids during the day; patients often report a history of recurrent dental caries. Parotid gland enlargement may occur in one-third of patients. Extraglandular manifestations widely vary in severity and organ system involvement. Some examples of extraglandular involvement include inflammatory arthritis, interstitial pneumonitis, primary biliary cirrhosis, peripheral neuropathy, small vessel vasculitis, and type 1 renal tubular acidosis. Patients who have primary SS are at increased risk for lymphoma, with a 44-fold increased incidence. Extranodal marginal zone B-cell lymphoma of mucosa-associated tissue is commonly seen. Clinical predictors of lymphoma are a history of cutaneous vasculitis; low C3 or C4 levels, or both; cryoglobulinemia; monoclonal gammopathy; and parotid gland enlargement.

KEY FACTS

- ✓ Scleroderma renal crisis is typically associated with progressive skin involvement, corticosteroid use that exceeds 15 mg/day, and other serious immunosuppression
- ✓ To avoid delay in appropriate treatment, clarify that the diagnosis is scleroderma renal crisis and not thrombotic thrombocytopenic purpura
- ✓ ACE inhibitors—can extend life expectancy in scleroderma renal crisis; therapy should be continued even when a patient's treatment progresses to dialysis
- ✓ Anti–Scl-70 may be present in SSc
- ✓ Primary SS—increases the risk of lymphoma 44-fold

Laboratory Findings

Most patients have a positive result for ANA in a speckled pattern. Approximately 65% to 75% of patients have a positive result for anti–SS-A antibody, and fewer patients (approximately 40% to 50%) have a positive result for anti–SS-B antibody. Detection of a polyclonal hypergammaglobulinemia is common because of increased B-cell activity and an elevated rheumatoid factor level. Cryoglobulins may be detected in approximately 30% of patients.

Diagnosis

Many criteria exist to diagnose SS. Most commonly used in clinical practice are the 2002 American-European Consensus Group classification criteria. They are dry eye symptoms; dry mouth symptoms; objective evidence of dry eyes (positive result of rose bengal, lissamine green, or Schirmer test); positive lymphocytic histopathologic findings on lip biopsy (focus score ≥1); objective evidence of decreased salivary flow, as seen with salivary scintigraphy; and presence of anti–SS-A or anti–SS-B antibody, or both.

Treatment

Management of glandular manifestations of SS involves symptomatic treatment of dry eyes with use of artificial tears, topical cyclosporine drops, and punctal occlusions. Dry mouth symptoms are treated with lubricating artificial saliva agents, liberal use of sugar-free candies to stimulate salivary flow, and muscarinic agonist medications, such as pilocarpine and cevimeline. Extraglandular manifestations may be treated with immunosuppressive agents in accordance with the extent of severity; corticosteroids, antimalarials, disease-modifying antirheumatic drugs, and rituximab have all been used.

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Musculoskeletal Disorders

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Neck Disorders

Diagnosis

Reports of cervicothoracic pain can be classified into 3 categories on the basis of their cause: mechanical, neurogenic, and pain secondary to other systemic processes.

Mechanical neck concerns are often secondary to trauma, overuse injury, malposture, and osteoarthritis. The pain is typically described as localized (spinal or paraspinal), dull, aching, and worse with range of motion. Physical examination often reveals point tenderness of the underlying spinous process and paraspinal musculature, as well as a decreased and painful range of motion.

Neurogenic neck concerns occur acutely after trauma or gradually as a result of progressive osteoarthritis with subsequent nerve root impingement (Figures 81.1 and 81.2). Classically, patients report an underlying dull, deep, and aching sensation with episodes of sharp, stabbing, and burning radicular symptoms. The radicular component is secondary to focal cervical nerve root impingement (Table 81.1), which can be reproduced on physical examination with use of the Spurling maneuver (Figure 81.3).

Neck pain *secondary to systemic disease* often is associated with systemic symptoms, such as fever, chills, weight loss, rash, polyarthralgia, or polymyalgia. The concomitant symptoms should help to guide the history, examination, and workup to elucidate the underlying illness.

Imaging studies, including plain radiography, computed tomographic myelography, and magnetic resonance imaging, are reserved for patients with antecedent trauma, progressive neurologic symptoms, and characteristics concerning for an underlying systemic process.

Treatment

Most patients with cervicothoracic concerns recover with conservative therapy. Treatments include medication (acetaminophen, nonsteroidal anti-inflammatory drugs [NSAID], and muscle relaxants), activity modification, soft cervical collar, and physical therapy. Opioids generally are not recommended, although they can be considered for a short duration for patients with acute moderate-severe pain. Symptoms that are ongoing despite these treatment modalities warrant consideration for corticosteroid injection. Intractable pain or progressive neurologic deficits warrant orthopedic consultation.

Lower Back Disorders

Diagnosis

Low back pain (LBP) is one of the most common presenting concerns in the primary care setting. Chronic LBP is the most common compensable work-related injury. Interestingly, LBP is generally a self-limited issue, with most patients noting improvement within 6 weeks.

The history and physical examination are essential in making the correct diagnosis. Only 3% of patients presenting with LBP have a cause that is not apparent after the initial history and examination (Tables 81.1 and 81.2). Arthritis (Figure 81.4), spinal stenosis, compression fracture, and malignancy are more commonly seen in older patients, whereas spondyloarthropathies are primarily seen before age 40 years. Physical examination should include assessment for spinal alignment, overlying skin changes, vertebral and paravertebral tenderness, and neurologic function, as well as straight-leg and crossed straight-leg raise tests. Pain must radiate below the knee when the leg is at 60° to 120° for a positive result (Figures 81.5).

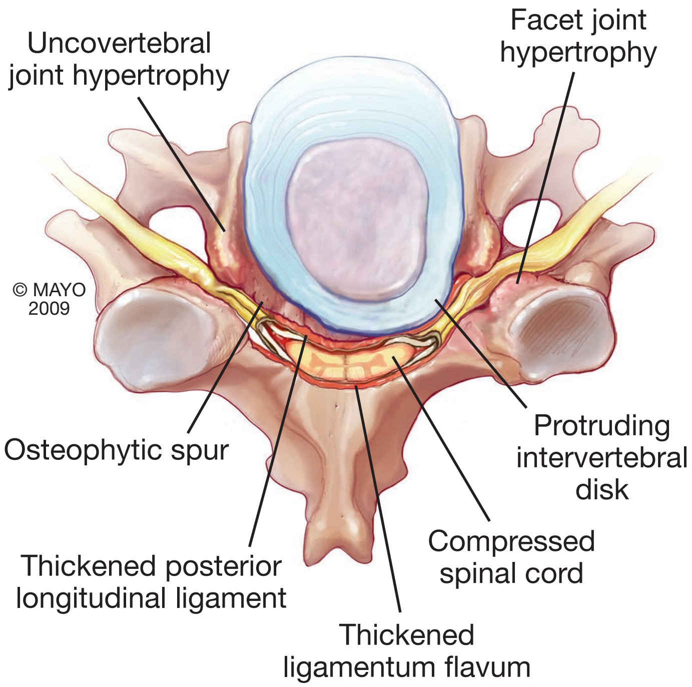
Uncovertebral joint hypertrophy
Facet joint hypertrophy
© MAYO 2009
Osteophytic spur
Protruding intervertebral disk
Compressed spinal cord
Thickened posterior longitudinal ligament
Thickened ligamentum flavum

Figure 81.1. *Anatomy of Neck Pain. Classic anatomical changes associated with neck pain.*

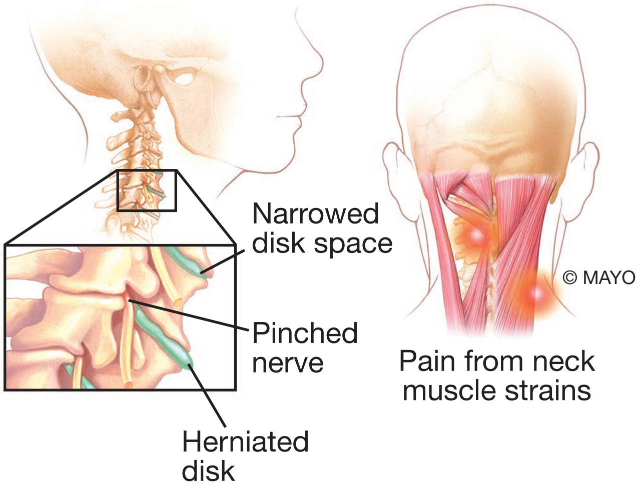
Narrowed disk space
Pinched nerve
Herniated disk
© MAYO
Pain from neck muscle strains

Figure 81.2. *Neurogenic and Muscular Neck Pain. Neurogenic and muscular sources of neck pain.*

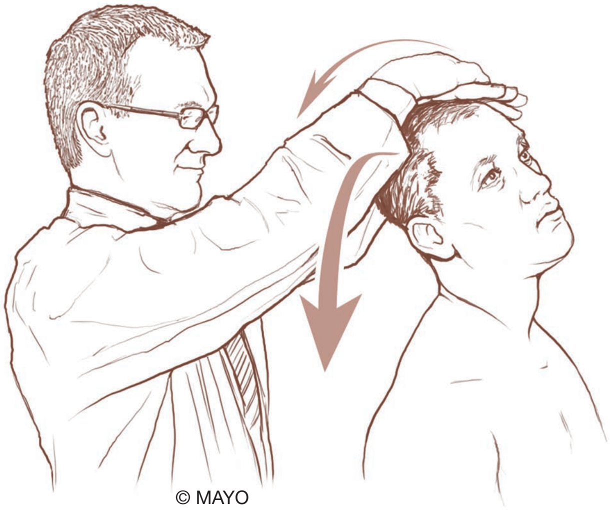

Figure 81.3. *Spurling Maneuver. Physical examination maneuver used to elicit cervical nerve root impingement.*

Table 81.1 • Neurologic Examination of the Spine

	Nerve Root							
Examination	**C5**	**C6**	**C7**	**C8**	**T1**	**L4**	**L5**	**S1**
Motor function	Deltoid, biceps	Biceps, wrist extensors	Triceps	Finger flexors	Intrinsic hand muscles	Quadriceps	Tibialis anterior	Gastrocnemius
Sensory function	Shoulder, lateral arm	Lateral forearm, thumb	Third digit	Medial forearm, fifth digit	Medial arm	Medial calf and ankle	Dorsal foot	Lateral ankle and foot
Reflex	Biceps	Biceps	Triceps	None	None	Knee	None	Ankle

Table 81.2 • Diagnostic Features of Low Back Pain

Diagnosis	Features
Nerve root disorder	Radiculopathy Sciatica Positive result on straight-leg test Positive result on crossed straight-leg test Provoked during Valsalva maneuver, cough, sneeze
Compression fracture	Advanced age History of osteoarthritis History of osteoporosis Trauma Corticosteroid use
Spinal stenosis	Impingement of lumbosacral cord Advanced age History of osteoarthritis Buttock and leg pain Pain with standing Relief with forward flexion and sitting Pseudoclaudication
Rheumatologic condition	Young to middle age Family history Morning stiffness Synovitis Polyarthritis
Infection	Fever Illicit drug use Cellulitis Urinary tract infection Other localizable infectious source
Cauda equina syndrome	Rapid neurologic deficits Saddle anesthesia Bowel and bladder dysfunction
Malignancy	Weight loss Nocturnal pain Pain at rest Worsening symptoms

Laboratory and imaging studies should be reserved for patients with concomitant red-flag signs and symptoms (Table 81.2). According to the joint guideline from the American College of Physicians and the American Pain Society, imaging should be obtained in cases of acute LBP only when associated with severe neurologic deficits or features that are concerning for a serious underlying condition. Common indications for spinal radiography are listed in Box 81.1.

KEY FACTS

- ✓ Mechanical neck concerns often result from trauma, overuse injury, bad posture, and osteoarthritis
- ✓ Neurogenic neck concerns may occur acutely after trauma or develop gradually from progressive osteoarthritis with nerve root impingement
- ✓ When neck pain is secondary to systemic disease, systemic symptoms (eg, fever, chills, weight loss) are often present
- ✓ LBP usually is self-limited and improves within 6 weeks
- ✓ Reserve laboratory and imaging studies for LBP for patients with red-flag signs or symptoms

Treatment

In the absence of concerning features, treatment of nonspecific LBP involves conservative therapy and reassurance. Conservative therapy involves medication (acetaminophen, NSAIDs, and muscle relaxants), activity modification, topical medicated agents, local ice and heat therapy, and physical therapy. Bed rest is no longer considered optimal care. Ongoing or radicular symptoms despite therapy warrant consideration for corticosteroid injection. Surgical intervention has documented clear benefit in cases of disk herniation with radiculopathy, cauda equina syndrome (surgical emergency), and severe spinal stenosis.

Shoulder Disorders

Diagnosis

Shoulder pain (Figures 81.6 and 81.7) may arise from intrinsic and extrinsic (referred) sources. An intrinsic (shoulder-specific) source is more likely when the patient has pain with range of motion and reports shoulder instability, locking, and catching. Common extrinsic sources include referred (radicular) pain from cervical nerve root disorders, gallbladder disease, cardiac ischemia, and apical pulmonary disease. Shoulder pain in younger patients is usually secondary to trauma or overuse. In older patients, shoulder concerns are likely to be due to degenerative or rotator cuff disorders. Common causes of shoulder disorders are reviewed in Table 81.3.

Examination of the shoulder should be undertaken systematically. Central components of the examination include visual inspection, palpation, range of motion maneuvers, and

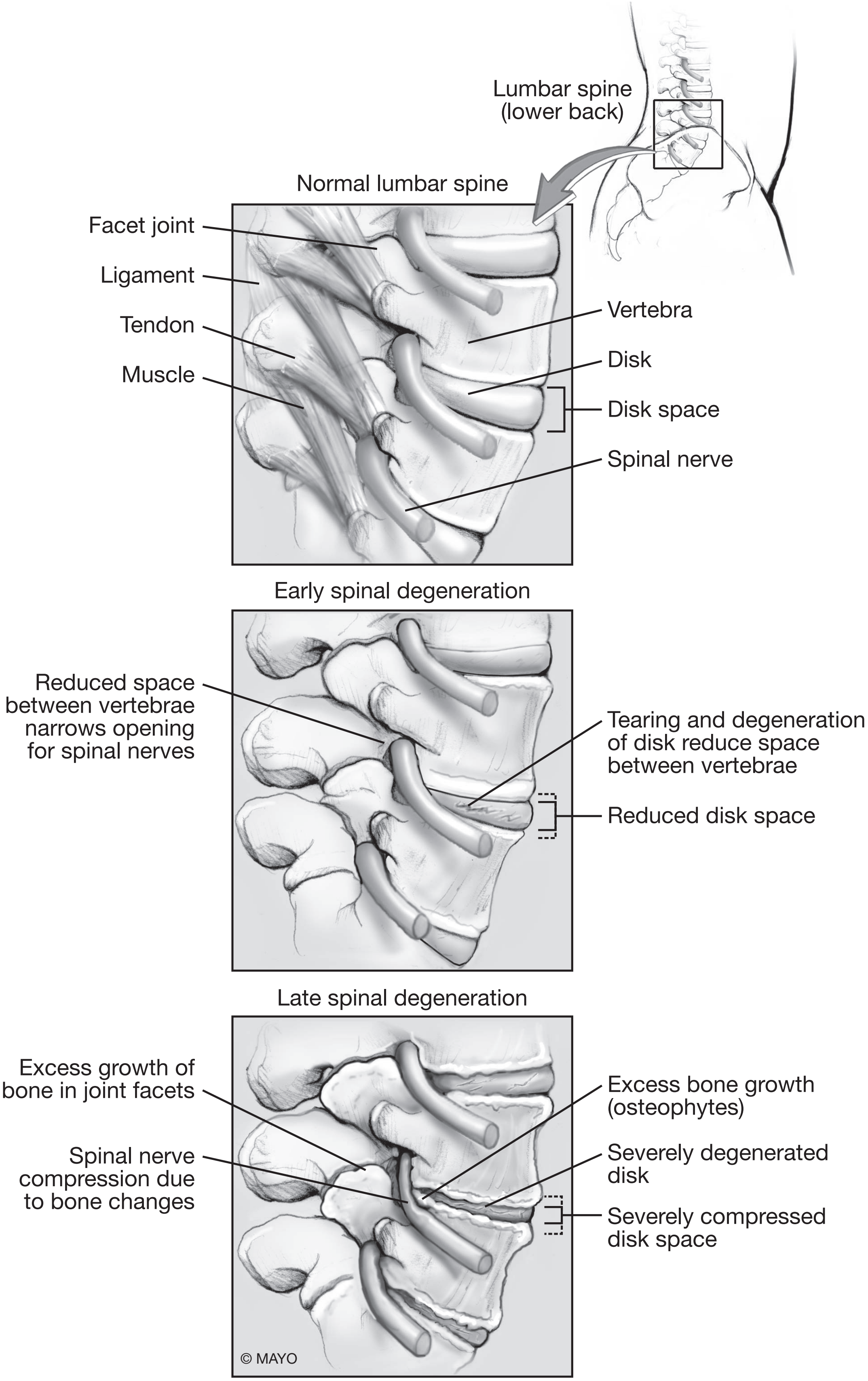
Lumbar spine
(lower back)
Normal lumbar spine
Facet joint
Ligament
Tendon
Muscle
Vertebra
Disk
Disk space
Spinal nerve
Early spinal degeneration
Reduced space between vertebrae narrows opening for spinal nerves
Tearing and degeneration of disk reduce space between vertebrae
Reduced disk space
Late spinal degeneration
Excess growth of bone in joint facets
Spinal nerve compression due to bone changes
Excess bone growth (osteophytes)
Severely degenerated disk
Severely compressed disk space
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Figure 81.4. *Anatomy of Low Back Pain. Classic anatomical changes associated with low back pain.*

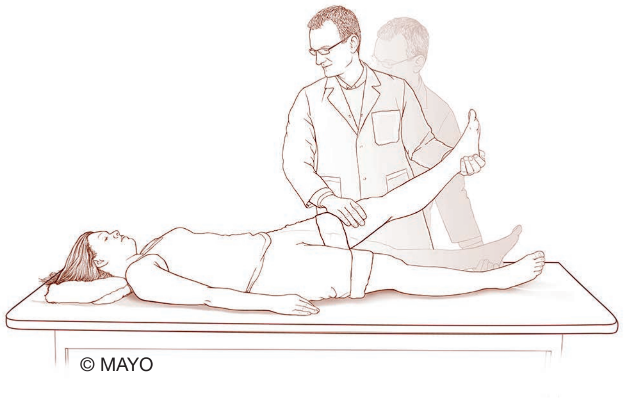


Figure 81.5. *Straight-Leg Test. Physical examination maneuver used to elicit the presence of lumbar disk herniation.*

provocative maneuvers (Table 81.4). Range of motion should be performed both passively and actively. Pain present during both active and passive range of motion is suggestive of an intra-articular source. In contrast, pain present only with active range of motion is more likely secondary to an extra-articular shoulder source (eg, ligament, tendon, bursa). Furthermore, pain during abduction exceeding 120° raises concern for acromioclavicular joint disease. Pain during abduction between 60° and 120° is more commonly associated with rotator cuff and bursal disease, most commonly due to an impingement syndrome.

In rotator cuff disorders, the supraspinatus tendon is most commonly affected. Impingement syndromes involving the rotator cuff are due to compression between the humeral head and acromion process; pain is classically worse with abduction. Weakness or a positive result of the drop-arm test is suggestive of a rotator cuff tear.

Adhesive capsulitis is secondary to progressive thickening of the glenohumeral joint capsule. Classically, this disorder is associated with prolonged immobilization (after injury or surgical operation), diabetes mellitus, trauma, hypothyroidism, and stroke. Patients have loss of both passive and active ranges of motion and frequently report ipsilateral pain when they lie on the affected side.

Treatment

Treatment recommendations are reviewed in Table 81.3. Strategies for acromioclavicular disease and bicipital tendinitis require modification of activities and NSAID use. Physical therapy, corticosteroid injection, and surgical interventions are usually reserved for refractory cases. Treatment of adhesive capsulitis requires prolonged physical therapy. Rotator cuff tendinitis and tear require a combination of rest, activity modification, physical therapy, and NSAIDs; corticosteroid injection and surgery are reserved for refractory cases.

Box 81.1 • Indications for Immediate Imaging in Acute Low Back Pain

Major risk factors for cancer (history of cancer, risk factors for cancer, or clinical concern/suspicion for cancer); radiograph preferred along with serum erythrocyte sedimentation rate (ESR)

Risk factors for spinal infection (fever, history of spinal infection, recent extraspinal infection, or intravenous illicit drug use); MRI preferred

Signs of or risk factors for cauda equina syndrome (saddle anesthesia, urinary retention/incontinence, or fecal retention/incontinence); MRI preferred

Severe or progressive neurologic signs or symptoms; MRI preferred

Abbreviation: MRI, magnetic resonance imaging.

Data from Chou R, Qaseem A, Snow V, Casey D, Cross JT Jr, Shekelle P, et al; Clinical Efficacy Assessment Subcommittee of the American College of Physicians; American College of Physicians; American Pain Society Low Back Pain Guidelines Panel. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007 Oct 2;147(7):478-91. Erratum in: Ann Intern Med. 2008 Feb 5;148(3):247-8.

Elbow Disorders

The most common and frequently encountered clinical syndromes of elbow pain are outlined in Table 81.5 and illustrated in Figures 81.8 and 81.9. Table 81.5 outlines evaluation and treatment of these disorders.

Hand and Wrist Disorders

Concerns involving the hand and wrist require a thorough history and examination (Table 81.6; Figures 81.10 through 81.12). History should include sites of involvement, symmetrical and asymmetrical nature, duration, presence of systemic symptoms, and history of antecedent trauma. Radiographs should be obtained in all cases of hand and wrist pain that involve antecedent trauma and localized tenderness to palpation, to exclude fracture. Delay in imaging and treatment of occult fracture can lead to serious morbidity, including avascular necrosis.

Hip Disorders

Diagnosis

Hip pain requires a methodical approach, given the joint's complexity and broad range of differential diagnoses. Numerous extra-articular and nonmusculoskeletal sources can refer pain to the hip. Therefore, a thorough evaluation of the hip should also include evaluation of the abdomen, genitalia, spine, and knee.

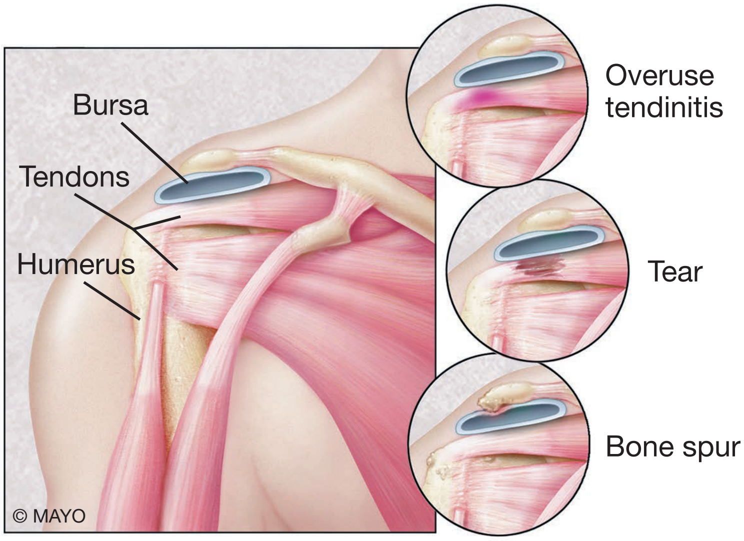


Figure 81.6. *Anatomy of Shoulder Pain, Part 1. Classic anatomical changes associated with shoulder pain.*

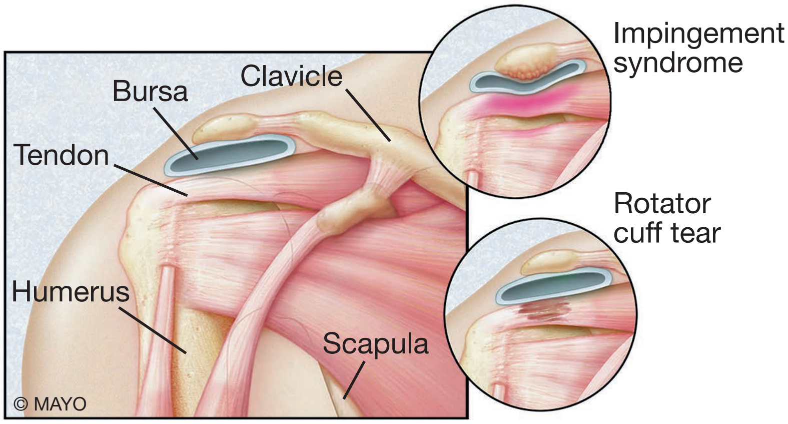


Figure 81.7. *Anatomy of Shoulder Pain, Part 2. Classic anatomical changes associated with shoulder pain.*

Table 81.3 • Shoulder Disorders

Consideration	Acromioclavicular Disease	Adhesive Capsulitis	Bicipital Tendinitis	Rotator Cuff Tendinitis/Tear
Cause	Trauma Overuse Osteoarthritis	Immobilization	Overuse Trauma	Overuse Trauma Recurrent tendinitis (tear)
Presentation	Pain at AC joint	Diffuse shoulder pain Decreased range of motion	Anterior shoulder and proximal arm pain	Anterolateral shoulder pain Lateral deltoid pain
Evaluation	Pain at AC joint with palpation Pain at AC joint with abduction >120° Positive result of cross-arm test	Limited and painful range of motion (active and passive)	Bicipital groove tenderness to palpation Positive results of Speed and Yergason tests	Pain with lateral palpation, abduction, internal and external rotation Positive results of impingement tests (Neer, Hawkins, and empty can) Positive drop-arm test (tear)
Treatment	Activity modification NSAIDs Corticosteroid injection Surgery	Physical therapy NSAIDs Corticosteroid injection Surgery	Rest Activity modification NSAIDs Corticosteroid injection Physical therapy	Rest Activity modification NSAIDs Corticosteroid injection Physical therapy Surgery (tear)

Abbreviations: AC, acromioclavicular; NSAID, nonsteroidal anti-inflammatory drug.

Table 81.4 • Shoulder Provocation Tests

Test	Maneuver	Positive Result	Diagnosis
Apley scratch test	Patient reaches overhead (arm flexion, shoulder external rotation and abduction) to reach for the superior aspect of the opposite scapula. With the other arm, patient reaches behind the back (arm extension, shoulder internal rotation and adduction) toward the inferior aspect of the opposite scapula	Loss of range of motion	Rotator cuff disorder
Apprehension test	Preferably while patient is supine, examiner passively abducts shoulder and elbow to 90°; applies slight anteriorly directed force to humerus and externally rotates shoulder	Patient has pain or apprehension (muscle guarding). Patient may feel clicking in anterior joint	Anterior glenohumeral joint instability
Clunk sign	While patient is supine, examiner passively abducts shoulder overhead; with 1 hand, holds distal humerus; places other hand on posterior glenohumeral joint and applies anteriorly directed force on joint while rotating humerus internally and externally	Clunk or grinding sound or sensation	Labral disorder
Cross-arm test	Shoulder flexion to 90° and active horizontal adduction	Pain in acromioclavicular joint	Acromioclavicular joint disorder
Drop-arm test	Examiner passively abducts shoulder to 90°; asks patient to slowly lower arm to waist	Uncontrolled lowering of arm	Rotator cuff tear (supraspinatus tendon)
Empty-can test	Shoulder abducted to 90° and horizontally adducted to 30° (into scapular plane); patient to point thumb downward as if emptying a can; examiner applies resisted downward pressure	Pain or weakness	Supraspinatus tendon impingement or tear
Hawkins test	Shoulder and elbow flexed to 90°; examiner forces internal rotation of shoulder	Pain	Supraspinatus tendon impingement or tear
Neer test	Internal rotation and passive flexion of arm to 180°	Passive painful arc	Subacromial impingement
Relocation test	Performed if positive result on apprehension test. Examiner applies posteriorly directed force on humerus while externally rotating arm	Decrease in or relief of symptoms from previous apprehension test	Anterior glenohumeral joint instability
Speed test	Shoulder flexion to 90°, forearm supinated; examiner applies resistance to shoulder flexion	Pain in bicipital groove	Bicipital tendinitis or instability
Spurling test	Cervical spine placed in extension with head rotated to affected shoulder while axially loaded	Radiating neck, shoulder, or arm pain	Cervical nerve root disorder
Sulcus sign	Downward traction applied to humerus	≥1 cm gap between humeral head and acromion	Inferior glenohumeral joint instability
Yergason test	Elbow flexion to 90°; forearm pronated; examiner applies resistance to forearm supination	Pain in bicipital groove	Bicipital tendinitis or instability

Specific Disorders and Treatment

The specific causes of hip pain are best categorized by the actual location of the pain: anterior, lateral, or posterior. Anterior hip pain, often experienced as groin pain, is most likely secondary to intra-articular osteoarthritis. Symptoms are frequently described as a dull, deep, aching sensation that is chronic in nature and worse with activity. Morning stiffness is often present. Other sources of anterior hip pain include fracture, osteonecrosis, and infection (septic arthritis), as well as referred pain from lumbar spinal disease, inguinal hernia, and other abdominopelvic sources.

Lateral hip pain is most frequently caused by trochanteric bursitis (Figure 81.13). Causes of trochanteric bursitis include overuse, obesity, trauma, and gait dysfunction. Patients have deep, aching lateral hip pain with intermittent radiation of pain to the buttock and lateral knee. Furthermore, patients report point tenderness at the site of the greater trochanter, especially during palpation and when lying on the affected side. Resisted hip abduction also reproduces the discomfort. Treatment options include rest, NSAIDs, physical therapy, corticosteroid injection, and surgery for refractory cases.

Meralgia paresthetica can cause anterolateral hip pain (Figure 81.14). This condition is due to entrapment of the lateral femoral cutaneous nerve at the level of the inguinal fold. Meralgia paresthetica is frequently associated with obesity, pregnancy, prolonged seated position, and tight-fitting clothing. Symptoms include pain over the anterolateral thigh

Table 81.5 • Common Elbow Disorders

Consideration	Lateral (Tennis) Epicondylitis	Medial (Golfer) Epicondylitis	Ulnar Neuropathy	Radial Neuropathy	Olecranon Bursitis
Cause	Overuse of wrist extensors and forearm supinators Trauma Computer use	Overuse of wrist flexors and forearm pronators Trauma	Trauma Repetitive movements Prolonged elbow resting	Overuse Trauma	Trauma Crystal arthropathy Infection Rheumatoid arthritis
Presentation	Lateral elbow pain with radiation down lateral forearm to dorsal hand	Medial elbow pain with radiation down medial forearm to palmar hand	Cubital tunnel syndrome Elbow pain and paresthesia with radiation down forearm to hand (ulnar distribution)	Proximal forearm pain and paresthesia with radiation to dorsal radial aspect of forearm and hand	Pain and swelling of elbow at bursal site
Evaluation	Lateral epicondyle pain with palpation Pain with forced wrist extension and forearm supination	Medial epicondyle pain with palpation Pain with forced wrist flexion and forearm pronation	Medial elbow pain and paresthesia with elbow flexion Ulnar distribution	Pain with resisted forearm supination Radial distribution	Inflamed olecranon bursa Pain with elbow flexion Fluid aspiration (crystal, Gram stain, culture)
Treatment	Rest Activity modification NSAIDs Corticosteroid injection Physical therapy Bracing Surgery	Same as for lateral epicondylitis	Activity modification NSAIDs Splinting Physical therapy Surgery	Same as for ulnar neuropathy	Treatment of underlying cause Activity modification

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

with concomitant sensory changes (paresthesia and dysesthesia) and tenderness over the inguinal ligament. Treatment includes weight loss, loose-fitting clothes, NSAIDs, physical therapy, and surgical release of the inguinal ligament in refractory cases.

Key Definition

Meralgia paresthetica: *neuropathy caused by entrapment of the lateral femoral cutaneous nerve at the level of the inguinal fold.*

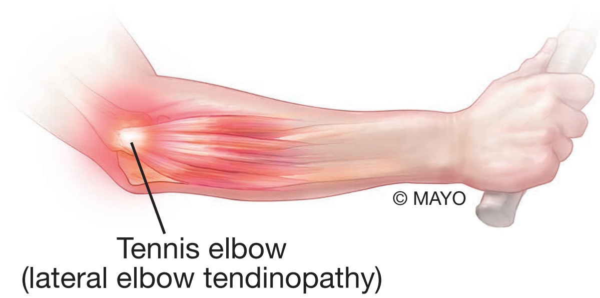


Figure 81.8. Tennis Elbow (Lateral Epicondylitis). Lateral elbow tendinopathy associated with tennis elbow.

Posterior hip pain is rarely due to an intra-articular source. Rather, posterior hip pain is frequently secondary to lumbosacral spine disease (back pain, paresthesia, and radiculopathy), sacroiliitis (point tenderness and gluteal pain), and piriformis syndrome (gluteal pain with radiculopathy that follows the sciatic nerve distribution). Plain radiography and magnetic resonance imaging are useful in making the diagnosis in cases of sacroiliitis and spinal disease.

Knee Disorders

Diagnosis

Knee pain is a common concern in clinical practice. Given the broad range of differential diagnoses (Tables 81.7 and 81.8; Figures 81.15 and 81.16), the history and physical examination are central to establishment of the correct diagnosis. The history should include location, chronicity, antecedent trauma, and presence of associated systemic symptoms. The proper knee examination should include bilateral visual inspection, palpation, range of motion, and applicable provocation tests. The anterior drawer and Lachman tests assess for defects of the anterior cruciate ligament. The posterior drawer test assesses for defects of the posterior cruciate ligament. The medial and lateral collateral ligaments can be assessed through applied valgus and varus stress, respectively. The McMurray and mediolateral grind tests can detect defects of the menisci. Imaging should be pursued in cases of trauma and cases in which examination results are suggestive of ligamentous or meniscal injury.

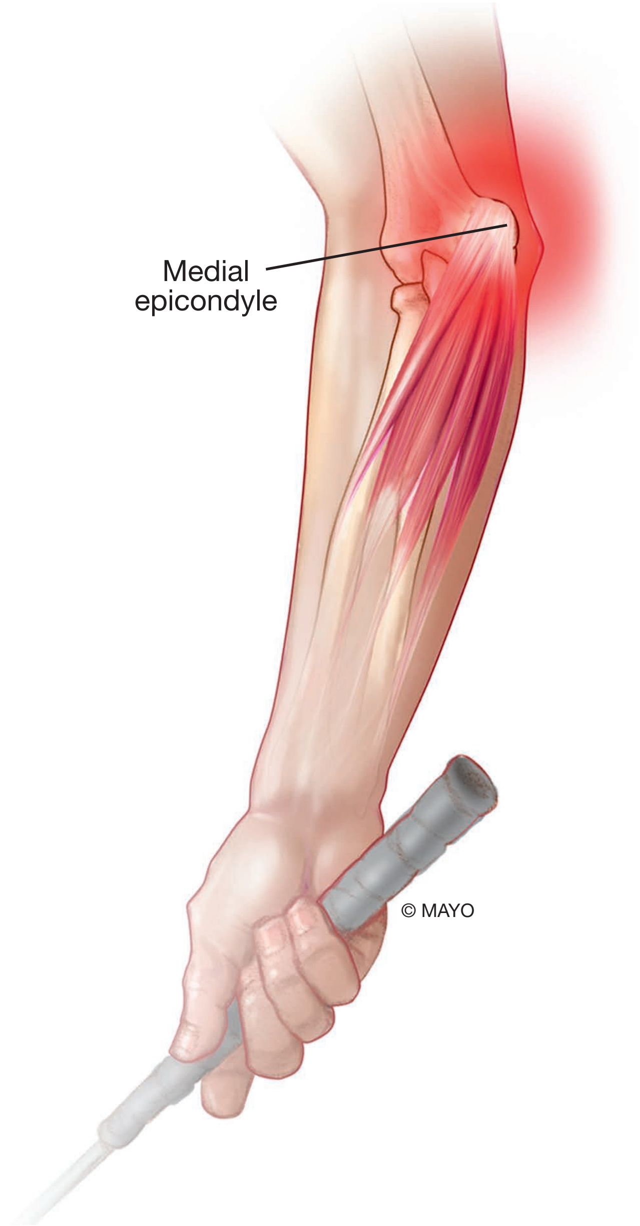


Figure 81.9. *Golfer's Elbow (Medial Epicondylitis). Medial elbow tendinopathy associated with golfer's elbow.*

KEY FACTS

- ✓ Rotator cuff disorders—most commonly affect the supraspinatus tendon
- ✓ Anterior hip pain—most likely due to intra-articular osteoarthritis; often manifested as groin pain
- ✓ Trochanteric bursitis—caused by overuse, obesity, trauma, and gait dysfunction
- ✓ Lateral hip pain may be caused by meralgia paresthetica
- ✓ Components of a proper knee examination—bilateral visual inspection, palpation, range of motion test, and applicable provocation tests

Treatment

Treatment recommendations are reviewed in Tables 81.7 and 81.8. In general, knee disorders are treated with a combination of rest, activity modifications, physical therapy, and NSAIDs. Corticosteroid injections, referral to orthopedic specialists, and surgical interventions are frequently required for treatment-refractory bursitis and osteoarthritis, as well as in cases of ligamentous and meniscal injury.

Ankle and Foot Disorders

Diagnosis

Successful diagnosis of ankle and foot disorders relies on localization of the focus of pain (Figure 81.17). Providers are well advised to separate ankle concerns from those of the foot, which in turn should be divided into concerns of the hindfoot, midfoot, and forefoot (Figure 81.18).

Ankle Disorders

Ankle concerns are generally secondary to trauma (sprain, strain, and fracture) and osteoarthritis. Trauma leading to an ankle sprain is usually due to traumatic inversion and plantar flexion, which most commonly lead to injury of the anterior talofibular ligament. Ankle sprains generally result in pain, swelling, stiffness, and possible instability; the severity of these symptoms helps to grade the degree of sprain. The history should include details of the mechanism of injury, and the examination should include visual inspection, palpation, and assessment for any limitations to range of motion or weight bearing. The need for imaging should be based on antecedent history, examination findings, and the Ottawa ankle rules (Figure 81.19). Treatment of low-grade sprains includes rest, ice, compression, elevation, and NSAIDs. Higher-grade sprains may require ankle stabilization, physical therapy, limitation of weight bearing, or surgical intervention.

Foot Disorders

Hindfoot pain primarily includes plantar fasciitis (Figure 81.20) and Achilles tendinopathy. Plantar fasciitis (inflammation of the plantar fascia) is caused by overuse and heel spurs, which lead to plantar foot and heel pain that classically is worse with the first few steps and improves with rest. Imaging is generally unnecessary. Treatment includes activity modification, plantar stretching, orthotics or proper footwear, NSAIDs, weight loss, corticosteroid injections, and surgical interventions in refractory cases. Achilles tendinopathy is commonly due to overuse, improper footwear, and fluoroquinolone use. Patients report tenderness along the tendon and painful foot dorsiflexion. Treatment includes activity modification and rest, heel lift, NSAIDs, and proper stretching. In Achilles tendon rupture, patients often have a popping or tearing sensation followed by inability to flex the foot, pain, swelling, and an abnormal Thompson test result (failure to plantar flex when the calf is squeezed). Diagnostic ultrasonography can also be used. Orthopedic evaluation is required for cases of tendon rupture.

Table 81.6 • Wrist and Hand Disorders

Consideration	Ganglion Cyst	Trigger Finger	Dupuytren Contracture	De Quervain Tenosynovitis	Carpal Tunnel Syndrome	Ulnar Tunnel Syndrome
Cause	Chronic irritation of wrist	Digital flexor tendon inflammation and stenosis	Palmar fascia contracture	Inflammation of abductor pollicis longus and extensor pollicis brevis tendons	Median nerve compression	Ulnar nerve compression
Risk factors	Advanced age Overuse Trauma	Overuse Diabetes mellitus Trauma Rheumatoid arthritis	Familial Diabetes mellitus Alcohol use disorder	Overuse Pregnancy	Overuse Obesity Pregnancy Hypothyroidism Diabetes mellitus Female sex	Overuse Trauma
Presentation	Swelling overlying wrist joints or tendons	Pain and catching sensation of digital flexor tendon	Flexed digits Difficulty with digital extension	Radial wrist pain when pinching or grasping with thumb	Pain and paresthesia in median nerve distribution Nocturnal symptoms Thenar wasting	Pain and paresthesia in ulnar nerve distribution
Evaluation	Palpable cystic swelling overlying wrist joint or tendons	Digital flexion with pain and palpable catch Palpable nodule along digital flexor tendon	Flexion deformity Palmar fascia thickening	Distal radial styloid process tenderness Finkelstein test	Hand symptom diagram Tinel and Phalen signs Nerve conduction test and EMG	Ulnar Tinel sign Nerve conduction test and EMG
Treatment	No intervention Injection (corticosteroid or hyaluronic acid) Surgery	Hand therapy Corticosteroid injection Surgery	Activity modification Hand therapy Surgery	Splinting Activity modification NSAIDs Corticosteroid injection Surgery	Activity modification Splinting NSAIDs Corticosteroid injection Surgery	Activity modification Splinting NSAIDs Surgery

Abbreviations: EMG, electromyography; NSAID, nonsteroidal anti-inflammatory drug.

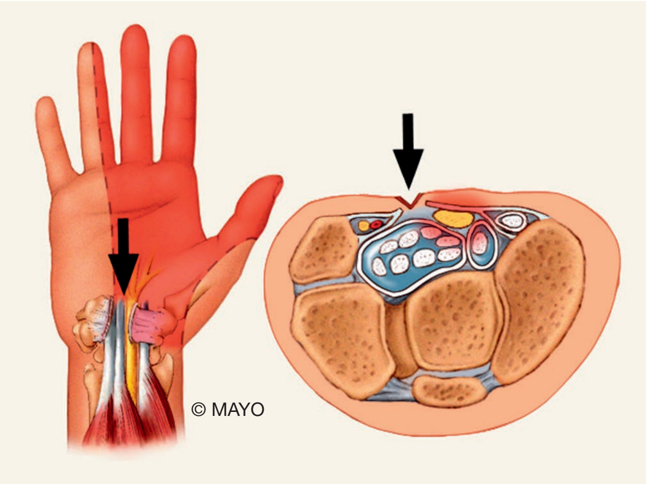
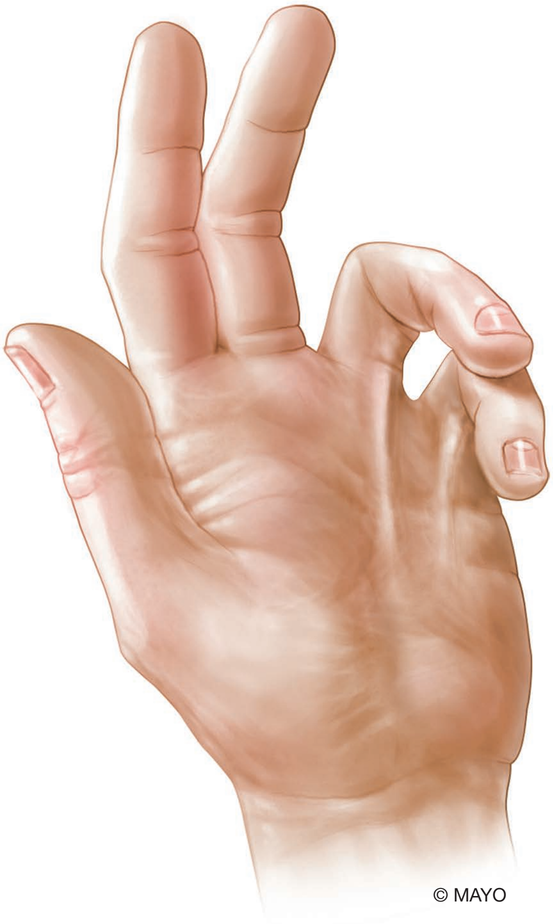


Figure 81.10. *Anatomy of Carpal Tunnel Syndrome. Anatomical changes associated with carpal tunnel syndrome, including nerve pattern distribution.*

Midfoot pain most commonly occurs with tarsal tunnel syndrome (entrapment of the posterior tibial nerve behind the medial malleolus). Symptoms include pain and paresthesia along the medial and plantar aspects of the foot, which are worsened with activity. Examination includes assessment for proper distribution of pain and paresthesia and the presence of a posterior medial malleolus Tinel sign. Treatment involves activity modification, orthotics, NSAIDs, and surgical intervention in refractory cases.

Forefoot concerns include Morton neuroma and hallux valgus. Morton neuroma (compression of common digital nerves) presents with pain and paresthesia most commonly between the third and fourth toes. This condition is commonly seen in persons who stand for prolonged periods and in women who wear high heels. Examination reveals focal tenderness and a palpable neuroma. Avoidance of high heels and prolonged standing, orthotics, corticosteroid injection, and NSAIDs are effective treatment options. Refractory cases may require surgical excision of the neuroma. Hallux valgus (bunion) development leads to pain at the first metatarsophalangeal joint,



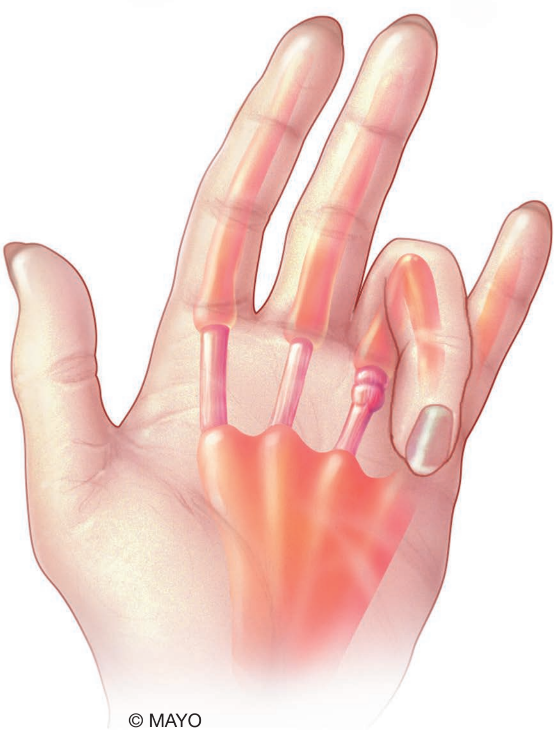


Figure 81.12. *Trigger Finger. Classic presentation of trigger finger.*

Figure 81.11. *Dupuytren Contracture. Classic presentation of Dupuytren contracture.*

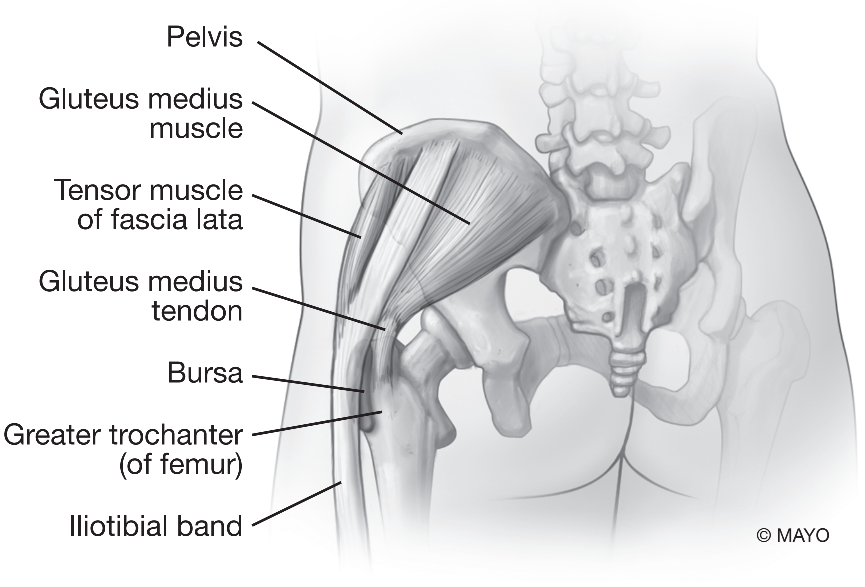

Pelvis
Gluteus medius muscle
Tensor muscle of fascia lata
Gluteus medius tendon
Bursa
Greater trochanter (of femur)
Iliotibial band
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Figure 81.13. *Anatomy of the Hip. Normal hip anatomy with applicable adjacent structures.*

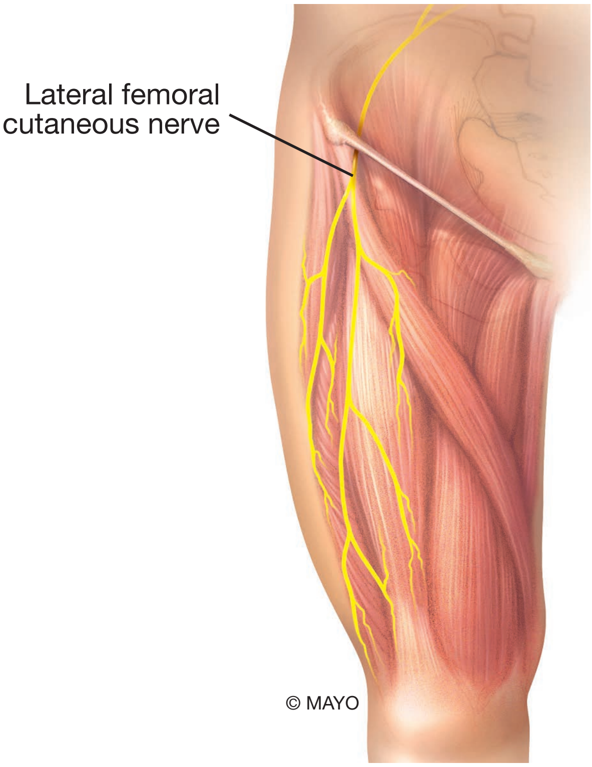

Figure 81.14. *Meralgia Paresthetica. Lateral femoral cutaneous nerve impingement leading to meralgia paresthetica.*

which worsens with activity, prolonged standing, and wearing high heels. Treatment options include proper footwear, activity modification, NSAIDs, orthotics, bracing, and surgical correction.

Fibromyalgia

Diagnosis

Fibromyalgia is a chronic centralized pain sensitivity syndrome, affecting up to 8% of the US population. The pathophysiologic basis for fibromyalgia is likely the dysregulation of the thalamus-hypothalamus-amygdala connection that leads to pain and sensory processing abnormalities (central sensitization). This results in pain signal generation, pain amplification, hyperalgesia, allodynia, and global sensory hypersensitivity. Recent evidence has also supported a genetic influence, with twin studies having shown a concordance rate up to 50%.

Key Definition

Fibromyalgia: *a chronic centralized pain sensitivity syndrome.*

The hallmark symptom of fibromyalgia is diffuse, multifocal, migratory, waxing and waning pain. The pain is primarily described as widespread arthralgia and myalgia. Concomitantly, patients often report fatigue, restless sleep, cognitive deficits

Table 81.7 • Knee Disorders: Osteoarthritis, Iliotibial Band Syndrome, Patellofemoral Pain, and Baker Cyst

Consideration	Osteoarthritis	Iliotibial Band Syndrome	Patellofemoral Pain	Baker (Popliteal) Cyst
Cause	Advanced age Overuse Obesity	Overuse	Degeneration of patellofemoral cartilage Overuse	Trauma (meniscal injury) Overuse Osteoarthritis Rheumatoid arthritis
Presentation	Pain with use; resolves with rest Morning stiffness	Lateral thigh/knee pain (above joint line); worse with steps	Anterior knee pain; worse with prolonged sitting and stair climbing	Pain and fullness in popliteal fossa
Evaluation	Joint line tenderness Decreased range of motion Effusion Crepitus Radiography	Noble test Tenderness at lateral femoral epicondyle	Patellofemoral compression test	Popliteal swelling, pain, fullness, and palpable effusion Possible ultrasonography to rule out DVT
Treatment	NSAIDs Acetaminophen Topical agents Physical therapy Corticosteroid injection Surgery	Rest NSAIDs Physical therapy Corticosteroid injection	Physical therapy (quadriceps strengthening) NSAIDs Ice Activity modification	Rest NSAIDs Elevation of leg Corticosteroid injection

Abbreviations: DVT, deep vein thrombosis; NSAID, nonsteroidal anti-inflammatory drug.

Table 81.8 • Knee Disorders: Bursitis, Ligament Injury, and Meniscal Injury

Consideration	Prepatellar Bursitis	Pes Anserine Bursitis	Anterior Collateral Ligament Injury	Posterior Cruciate Ligament Injury	Collateral Ligament Injury	Meniscal Injury
Cause	Frequent sustained pressure with knee flexed Trauma Infection Gout	Overuse (running, uphill climbing, cycling) Trauma Valgus knee deformity Osteoarthritis	Trauma Knee twisting injury with foot planted	Trauma (dashboard injury) Knee hyperextension injury	Overuse Trauma	Overuse Trauma
Presentation	Pain, swelling, erythema of anterior knee	Anteromedial knee/leg pain (below medial joint line)	Acute-subacute onset of pain, swelling, and instability	Acute-subacute onset of pain, swelling, and instability	Medial or lateral knee pain	Knee joint line pain Knee lock, buckle, catch, pop
Evaluation	Tenderness, erythema, and pain of prepatellar bursa Aspiration (gout vs infection)	Tenderness at anserine bursa Pain with knee flexion and squatting	Anterior drawer test Lachman test	Posterior drawer test	Varus (lateral collateral) stress test Valgus (medial collateral) stress test	Joint line tenderness Medial-lateral grind test McMurray test
Treatment	Rest Activity modification NSAIDs Treatment of gout or infection	Activity modification Rest NSAIDs Corticosteroid injection	Orthopedic evaluation	Orthopedic evaluation	Rest NSAIDs Physical therapy Orthopedic evaluation	Rest NSAIDs Physical therapy Orthopedic evaluation

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

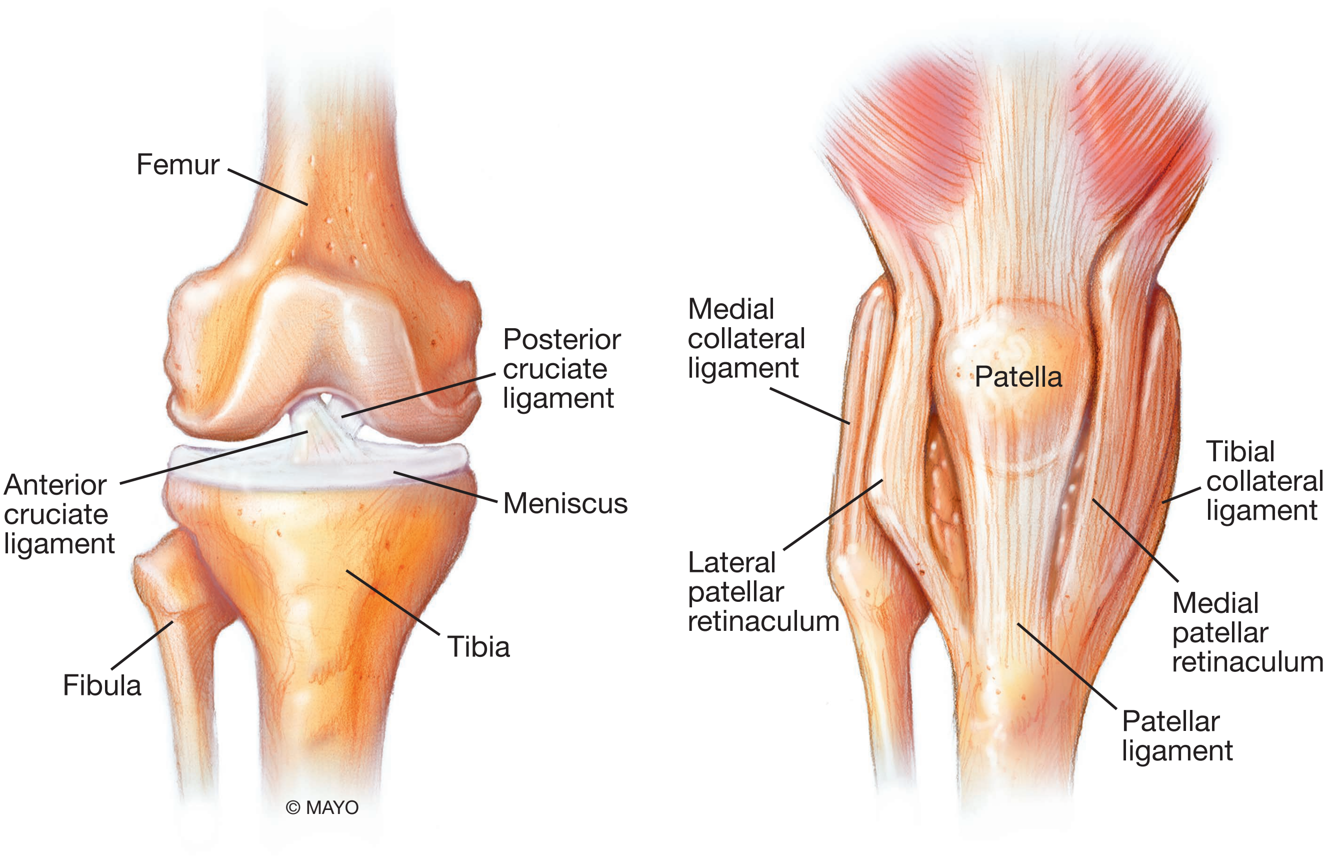
Femur
Posterior cruciate ligament
Anterior cruciate ligament
Meniscus
Tibia
Fibula
© MAYO
Medial collateral ligament
Patella
Tibial collateral ligament
Lateral patellar retinaculum
Medial patellar retinaculum
Patellar ligament

Figure 81.15. *Anatomy of the Knee, Anterior View. Normal anterior knee anatomy with applicable adjacent structures.*

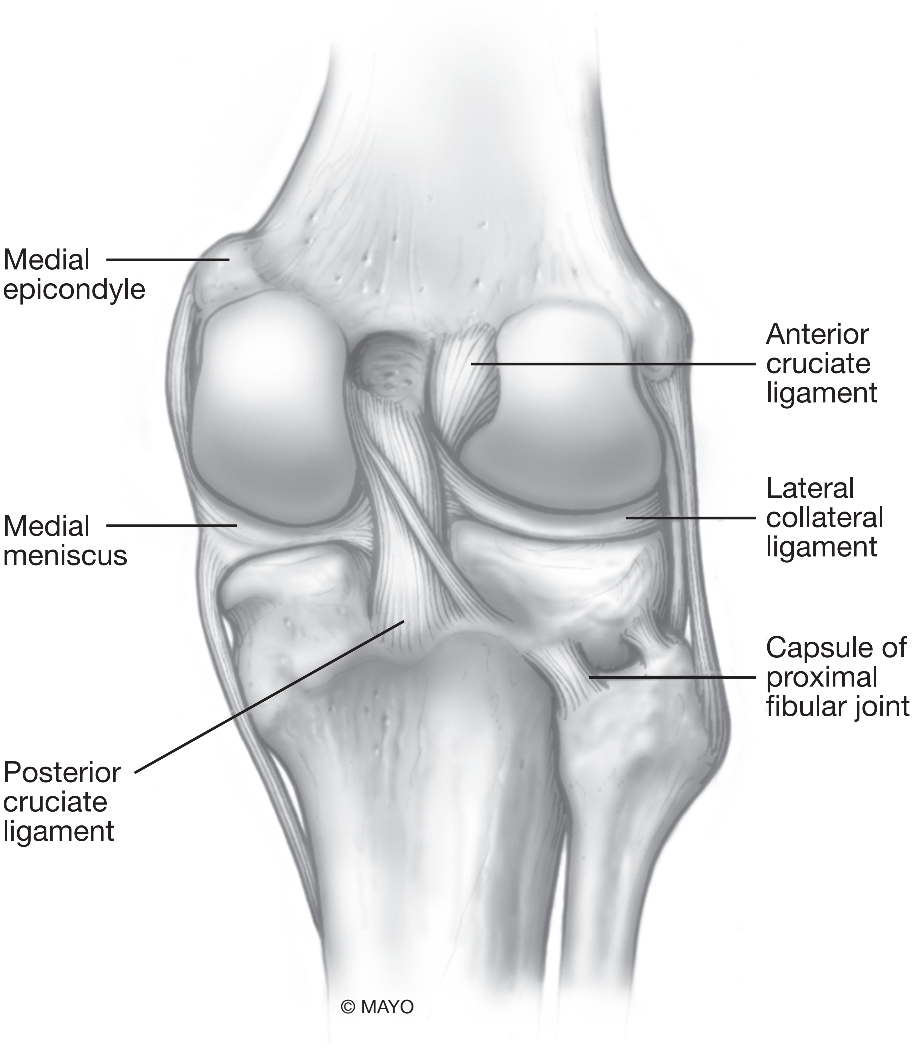
Medial epicondyle
Anterior cruciate ligament
Lateral collateral ligament
Medial meniscus
Capsule of proximal fibular joint
Posterior cruciate ligament
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Figure 81.16. *Anatomy of the Knee, Posterior View. Normal posterior knee anatomy with applicable adjacent structures.*

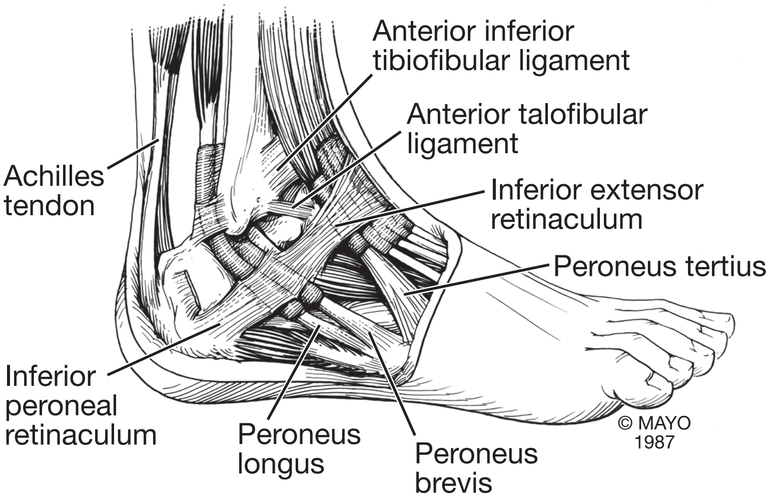
Anterior inferior tibiofibular ligament
Anterior talofibular ligament
Achilles tendon
Inferior extensor retinaculum
Peroneus tertius
Inferior peroneal retinaculum
Peroneus longus
Peroneus brevis
© MAYO 1987

Figure 81.17. *Anatomy of the Foot and Ankle, Lateral View. Normal lateral foot and ankle anatomy with emphasis on tendinous and ligamentous structures.*

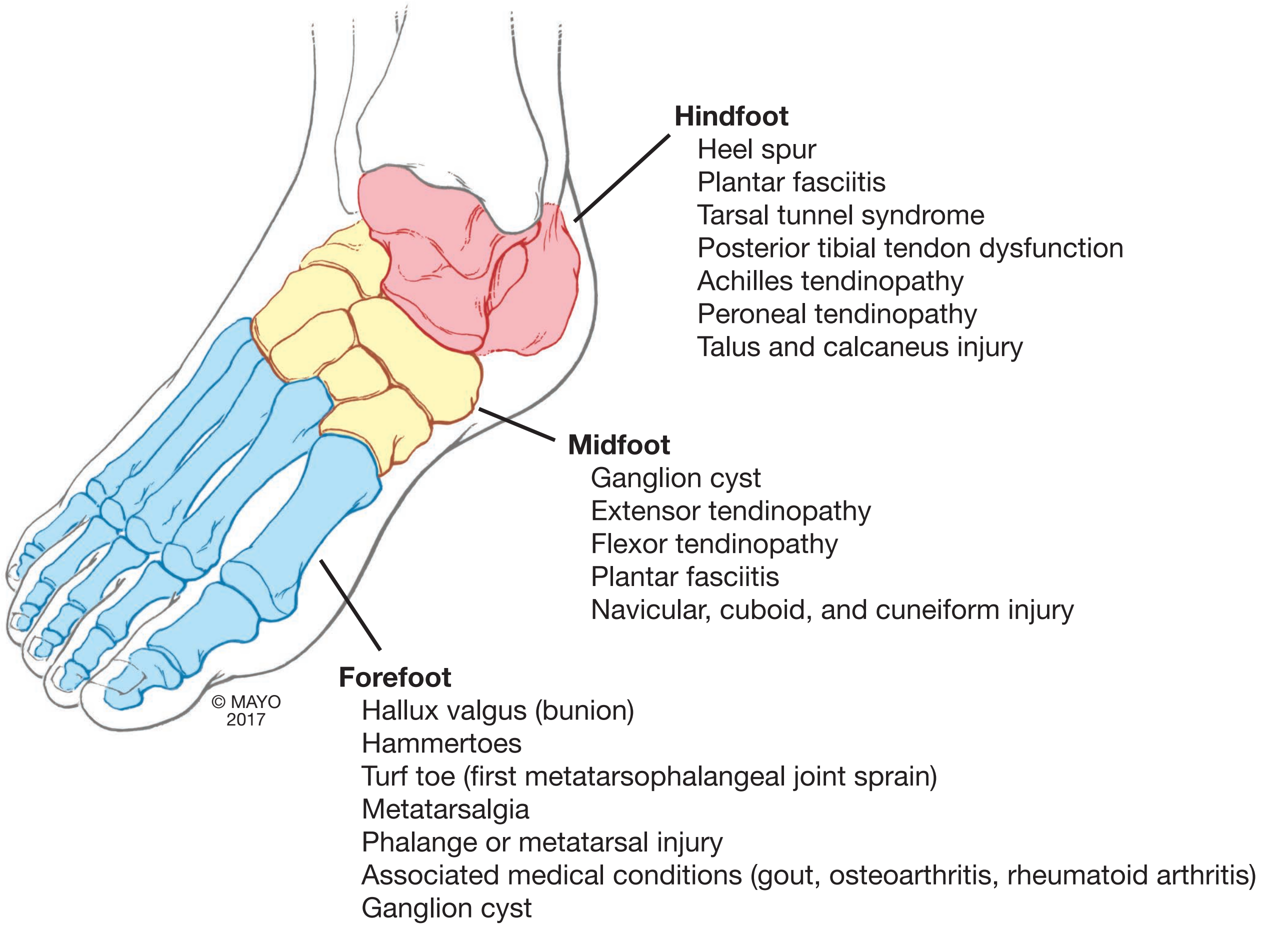
Hindfoot
Heel spur
Plantar fasciitis
Tarsal tunnel syndrome
Posterior tibial tendon dysfunction
Achilles tendinopathy
Peroneal tendinopathy
Talus and calcaneus injury
Midfoot
Ganglion cyst
Extensor tendinopathy
Flexor tendinopathy
Plantar fasciitis
Navicular, cuboid, and cuneiform injury
Forefoot
Hallux valgus (bunion)
Hammertoes
Turf toe (first metatarsophalangeal joint sprain)
Metatarsalgia
Phalange or metatarsal injury
Associated medical conditions (gout, osteoarthritis, rheumatoid arthritis)
Ganglion cyst
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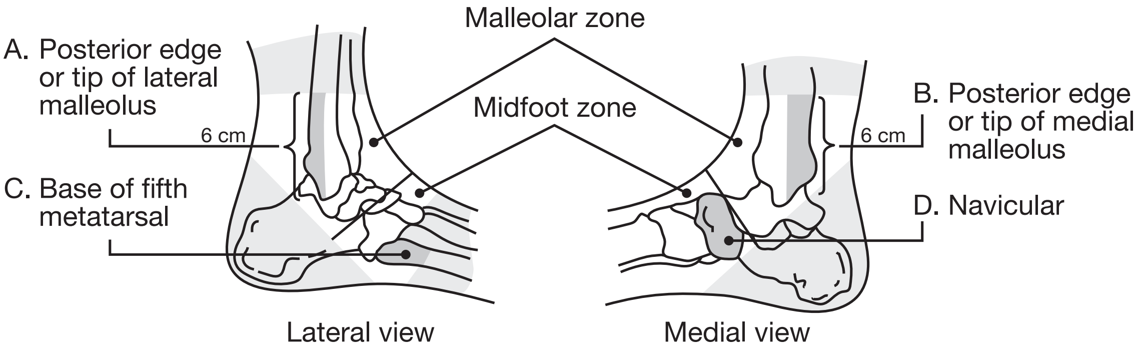
Figure 81.18. *Foot Regions and Diagnoses.*


Malleolar zone
A. Posterior edge or tip of lateral malleolus
6 cm
Midfoot zone
B. Posterior edge or tip of medial malleolus
6 cm
C. Base of fifth metatarsal
D. Navicular
Lateral view
Medial view

An ankle radiographic series is only required if there is any pain in malleolar zone and any of these findings:

1. Bone tenderness at A or
2. Bone tenderness at B or
3. Inability to bear weight both immediately and in emergency department

A foot radiographic series is only required if there is any pain in midfoot zone and any of these findings:

1. Bone tenderness at C or
2. Bone tenderness at D or
3. Inability to bear weight both immediately and in emergency department

Figure 81.19. *Ottawa Ankle Rules. Risk stratification strategies to determine the need for imaging for patients with acute ankle injury.* (From Stiell IG, McKnight RD, Greenberg GH, McDowell I, Nair RC, Wells GA, et al. Implementation of the Ottawa ankle rules. JAMA. 1994 Mar 16;271[11]:827-32; used with permission.)

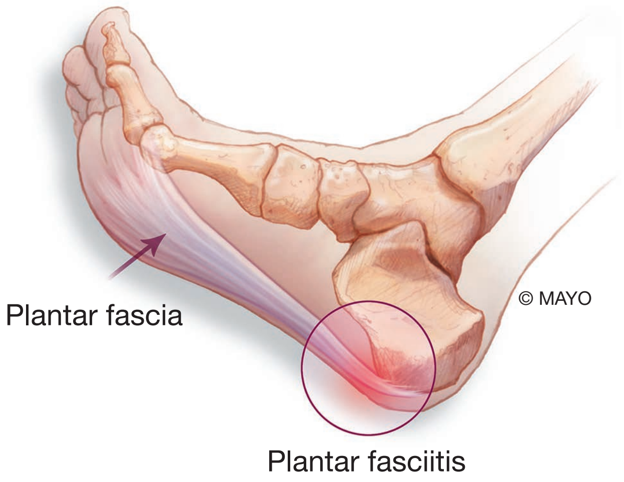


Figure 81.20. *Anatomy of Plantar Fasciitis. Distribution of plantar fascia and associated fasciitis.*

("brain fog"), and other somatic symptoms. Most patients also have depression or anxiety.

In 1990, the American College of Rheumatology put forth the initial diagnostic criteria for fibromyalgia. A thorough tender point examination was required, and the diagnosis was confirmed when 11 or more (of 18) tender points were present (Figure 81.21). In 2010, the American College of Rheumatology revised the diagnostic criteria to implement a global symptomatic approach. Current diagnostic criteria require pain symptoms for 3 months or longer; widespread pain index score of 7 or greater (the body is divided into 19 areas, with 1 point given for each painful area) and symptom severity score of 5 or higher (rated scale of symptoms that include fatigue, restless sleep, cognitive concerns, and somatic symptoms); and symptoms not due to another underlying cause.

Treatment

Treatment of fibromyalgia requires a multifaceted approach with the implementation of nonmedication and medication options. Compared with medication options, nonmedication treatments have been shown to be superior in efficacy and to have longer-lasting effects. These options include ongoing patient education, implementation of a graded aerobic exercise program, dietary modifications, physical therapy, occupational therapy, cognitive behavioral therapy, biofeedback therapy, and sleep hygiene.

The currently approved agents to treat fibromyalgia are serotonin-norepinephrine reuptake inhibitors (duloxetine and milnacipran) and pregabalin. Opioids should be avoided owing to their lack of benefit in fibromyalgia, propensity to lead to opioid-induced hyperalgesia, abuse potential, and adverse effect profile.

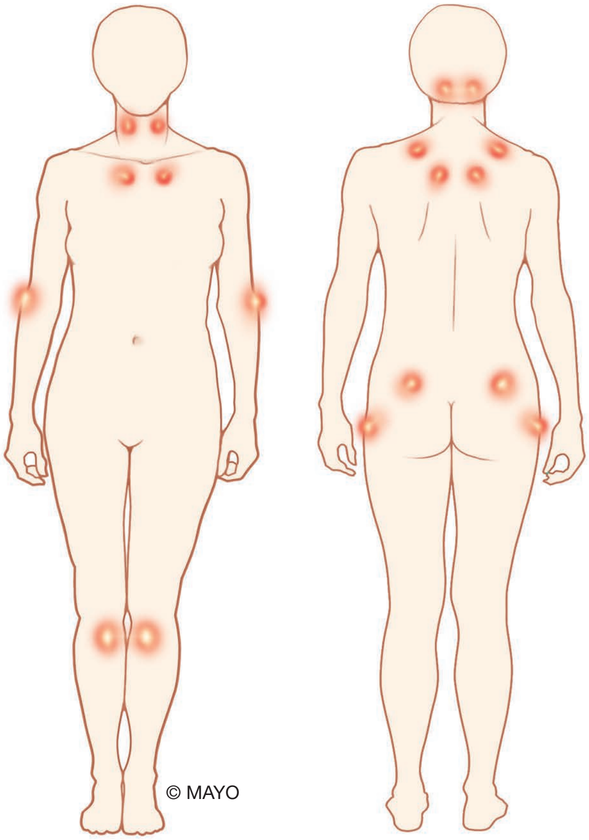


Figure 81.21. *Fibromyalgia. Location of tender points associated with fibromyalgia.*

KEY FACTS

- ✓ Main causes of hindfoot pain—plantar fasciitis and Achilles tendinopathy
- ✓ Midfoot pain—most common with tarsal tunnel syndrome
- ✓ Forefoot pain—Morton neuroma and hallux valgus
- ✓ The hallmark symptom of fibromyalgia—diffuse, multifocal, migratory, waxing and waning pain
- ✓ Fibromyalgia requires multifaceted treatment, including both medication and nonmedication options

82

Osteoarthritis, Gout, and Inflammatory Myopathies

FLORANNE C. ERNSTE, MD

Osteoarthritis

Osteoarthritis is the failure of articular cartilage and the subsequent degenerative changes in subchondral bone, bony joint margins, synovium, and para-articular fibrous and muscular structures. Osteoarthritis is the most common joint disease. Of patients, 80% have some limitation of their activities, and 25% are unable to perform major activities of daily living. As a consequence, osteoarthritis is a substantial economic burden to society. The prevalence of osteoarthritis is strongly associated with aging. Joints most commonly affected are the knee, hand, spine, metatarsophalangeal, and hip joints. Radiologic evidence of the disease greatly exceeds the prevalence of symptomatic cases.

> Key Definition
>
> **Osteoarthritis:** *the failure of articular cartilage and the subsequent degenerative changes in subchondral bone, bony joint margins, synovium, and para-articular fibrous and muscular structures.*

Pathogenesis

Two principal changes associated with osteoarthritis are the progressive focal degeneration of articular cartilage and the formation of new bone (osteophytes) in the floor of the cartilage lesion at the joint margins. Osteoarthritis represents the interaction of multiple genetic and environmental factors. Not all mechanisms that cause osteoarthritis have been identified. Current theories include a mechanical process (cartilage injury, particularly after impact loading) and a biochemical process (failure of cartilage repair processes to adequately compensate for injury). A combination of mechanical and biochemical processes likely contributes in most cases of osteoarthritis. It must be emphasized that osteoarthritis is not just the consequence of the wear and tear of aging. For example, a person who is prone genetically to generalized osteoarthritis may show premature disease in a knee that is related to obesity or trauma.

Clinical Features

The pain of an osteoarthritic joint is usually described as a deep ache. Subchondral bone edema contributes to the discomfort. The pain occurs with joint use and is relieved with rest and cessation of weight bearing. As the disease progresses, the involved joint may be symptomatic with minimal activity or even at rest. The pain originates in the structures around the disintegrating cartilage (cartilage has no nerves). The joint may be stiff with initial use, but this initial stiffness is not prolonged because osteoarthritis is an inflammatory arthritis, such as rheumatoid arthritis. Although the symptoms are related predominantly to mechanical failure and motion limits, joint debris and the associated repair process promote mild inflammation, accumulation of synovial fluid, and mild hypertrophy of the synovial membrane. Acute inflammation can transiently occur at Heberden nodes (distal interphalangeal joints with prominent osteophytes as a consequence of osteoarthritis) or at the knee with tearing of a degenerative meniscal cartilage. The pain of osteoarthritis is never generalized, but typically it is limited to a few joints at any given time. A new superimposed

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The editors and author acknowledge the contributions of Clement J. Michet, MD, to the previous edition of this chapter.

illness should be considered in an elderly osteoarthritic patient who presents with generalized musculoskeletal pain. Typical scenarios include polymyalgia rheumatica and late-onset rheumatoid arthritis.

Physical examination documents joint margin tenderness, fine crepitus, limits to motion, and enlargement of the joint. The enlargement is usually bony (proliferation of cartilage and bone to form osteophytes), but it can include effusions and mild synovial thickening. Deformity is a late consequence of the osteoarthritis and is associated with atrophy or derangement of the local soft tissues, ligaments, and muscles. Radiographic or physical examination evidence of the severity of osteoarthritis does not reliably predict a patient's symptoms.

Clinical Subsets

Primary Osteoarthritis

Primary osteoarthritis is cartilage failure without a known cause that would predispose to osteoarthritis. It almost never affects the shoulders, elbows, ankles, metacarpophalangeal joints, or ulnar side of the wrist. Primary osteoarthritis is divided into several clinical patterns.

Generalized osteoarthritis involves the distal interphalangeal joints, proximal interphalangeal joints, first carpometacarpal joints, hips, knees, and spine (Figure 82.1). It occurs most frequently in middle-aged postmenopausal women.

Isolated nodal osteoarthritis is primary osteoarthritis that affects only the distal interphalangeal joints. It occurs predominantly in women and has a familial predisposition. Isolated involvement at the base of the thumb is also common.

Isolated hip osteoarthritis is more common in men than women. It has no clear association with obesity or activity. Many cases are now thought to be related to mild joint developmental structural abnormalities such as femoral acetabular impingement.

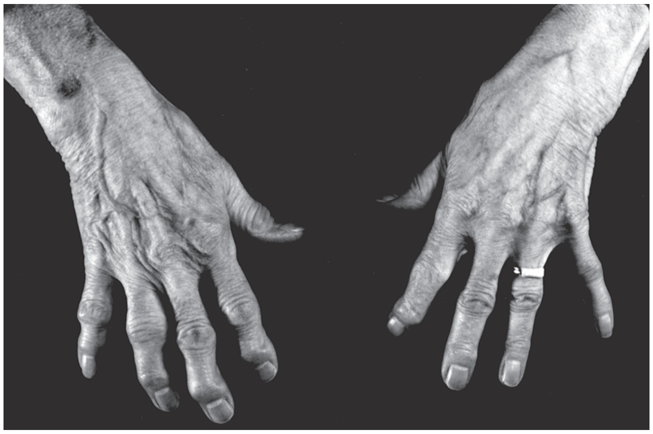

Figure 82.1. *Generalized Osteoarthritis. Of note, prominent bony hypertrophy is seen at the proximal (Bouchard nodes) and distal (Heberden nodes) interphalangeal joints. The metacarpophalangeal joints are spared. Early hypertrophic changes are seen on profile at the first carpometacarpal joint, giving a slight squaring of the hand deformity, appreciated best in this patient's left hand.*

Erosive osteoarthritis affects only the distal and proximal interphalangeal joints. Patients with erosive osteoarthritis have episodes of local inflammation. Mucous cyst formation at the distal interphalangeal joint is common. Painful flare-up of the disease recurs for years. Bony erosions and collapse of the subchondral plate—characteristics not usually seen in primary osteoarthritis—with osteophytes are markers of erosive osteoarthritis. Angular joint deformity can be severe. Bony ankylosis develops in many cases and is usually associated with relief of pain. This condition may be confused with rheumatoid arthritis, but unlike rheumatoid arthritis, erosive osteoarthritis never affects the metacarpophalangeal or wrist joints.

Diffuse idiopathic skeletal hyperostosis (DISH), also known as *Forestier disease*, is a diffuse ossification and calcification process involving ligaments and entheses. It occurs chiefly in men older than 50 years. The diagnosis requires the finding of characteristic exuberant, flowing osteophytes that connect 4 or more vertebrae with preservation of the disk space. DISH is radiographically distinguished from typical osteoarthritis of the spine with degenerative disk disease and from ankylosing spondylitis. Extraspinal sites of disease involvement include calcification of the pelvic ligaments, exuberant osteophytosis at the site of peripheral osteoarthritis, well-calcified bony spurs at the calcaneus, and heterotopic bone formation after total joint arthroplasty. Patients with DISH are often obese, and 60% have diabetes mellitus or glucose intolerance. Symptoms include mild back stiffness and, occasionally, back pain. Pathologically and radiologically, DISH is distinct from other forms of primary osteoarthritis.

Key Definition

Diffuse idiopathic skeletal hyperostosis: *a diffuse ossification and calcification process involving ligaments and entheses; also known as Forestier disease.*

Secondary Osteoarthritis

Secondary osteoarthritis is a progressive loss of articular cartilage in unusual distributions (ie, shoulders, wrists, metacarpophalangeal joints, and ankles) that results in degenerative changes and joint failure. Table 82.1 lists some major examples of inherited disorders of connective tissue that predispose to premature or secondary osteoarthritis, including their gene defects and characteristics. For example, Ehlers-Danlos syndrome comprises a rare group of genetic disorders characterized by tissue fragility, skin hyperextensibility, and joint hypermobility; Marfan syndrome is a similar rare genetic syndrome characterized by joint hypermobility and morphologic features of pectus excavatum or pectus carinatum, scoliosis, and disproportionately long extremities. Some metabolic abnormalities that can cause secondary osteoarthritis are ochronosis, hemochromatosis, Wilson disease, and acromegaly. Additionally, Paget disease of bone, involving the femur or pelvis about the hip joint, can predispose to secondary osteoarthritis.

Key Definition

Secondary osteoarthritis: *a progressive loss of articular cartilage resulting in degenerative changes and joint failure from traumatic, congenital, metabolic, neuropathic, or inflammatory causes.*

Joint trauma or chronic joint injury also can cause secondary osteoarthritis. The pathogenesis involves stress from repeated impact loading that weakens subchondral bone. Internal joint derangement with ligamentous laxity or meniscal damage alters the normal mechanical alignment of the joint. Chronic rotator cuff tear with subsequent loss of shoulder joint cartilage (ie, rotator cuff arthropathy) and knee osteoarthritis that develops years after meniscal cartilage damage are examples of chronic injury leading to secondary osteoarthritis.

Developmental malformations of joints, such as congenital hip dysplasia, femoral acetabular impingement, and epiphyseal dysplasia, lead to premature or secondary osteoarthritis (Table 82.1). Pediatric joint or bone injuries, such as slipped capital femoral epiphysis and Legg-Calvé-Perthes disease (idiopathic avascular necrosis of the femoral head), result in premature or secondary osteoarthritis in young adults.

Hemochromatosis Arthropathy

Hereditary hemochromatosis is an autosomal recessive disorder caused by abnormal iron absorption and subsequent iron overload due to point mutations. Most patients are homozygous for C282Y/C282Y, although 5% may be compound heterozygous for the mutations C282Y/H63D of the *HFE* gene on chromosome 6. The compound heterozygous form of the disease is commonly associated with arthropathy.

The classic clinical spectrum of hemochromatosis includes hepatomegaly, bronze skin pigmentation, diabetes mellitus, hypogonadism, cardiomyopathy, and degenerative arthritis. Diabetes, hypogonadism, and cardiomyopathy are considered rare and late manifestations of hemochromatosis. The arthropathy can be an initial manifestation and eventually affects most patients. It symmetrically involves the second and third metacarpophalangeal joints and large joints that are not typically affected by generalized primary osteoarthritis.

Hemochromatosis arthropathy should be considered in patients younger than 50 years who present with pseudogout or chondrocalcinosis. The iron screening tests look for increased transferrin saturation and elevated serum ferritin levels. Radiographs may show chondrocalcinosis and hooklike osteophytes of affected joints such as the metacarpophalangeal joints, as well as uniform

Table 82.1 • Inherited Disorders of Connective Tissue

Condition	Gene Defect	Characteristics
Marfan syndrome (autosomal dominant)	Fibrillin gene (*FBN1*)	Hypermobile joints: osteoarthritis, arachnodactyly, kyphoscoliosis Lax skin, striae, ectopic ocular lens Aortic root dilatation (aortic insufficiency), mitral valve prolapse, aneurysms, and aortic dissection
Ehlers-Danlos syndrome (10 subtypes)	Collagen gene (*COL5A1*, *COL5A2*)	Joint hypermobility, friable skin, secondary osteoarthritis; type IV associated with vascular aneurysms
Osteogenesis imperfecta (autosomal dominant and recessive variations; the most common heritable disorder of connective tissue, 1:20,000; 4 subtypes)	Type I collagen gene	Brittle bones, blue sclerae, otosclerosis and deafness, joint hypermobility, and tooth malformation
Type II collagenopathies Achondrogenesis type II Hypochondrogenesis Spondyloepiphyseal dysplasia Spondyloepimetaphyseal dysplasia Kniest dysplasia Stickler syndrome Familial precocious osteoarthropathy	Type II collagen gene	Spectrum from lethal (achondrogenesis) to premature osteoarthritis (Stickler syndrome, characterized by craniofacial abnormalities [eg, micrognathia, cleft palate], myopia, retinal detachment, hearing loss, joint laxity)
Achondroplasia (autosomal dominant)	Fibroblast growth factor III receptor gene	Dwarfism, premature osteoarthritis
Pseudoachondroplasia	Cartilage oligomeric matrix protein (*COMP*) gene	Short stature, premature osteoarthritis

joint space narrowing, sclerosis, and subchondral cystic changes. On radiographs, chondrocalcinosis is occasionally seen superimposed on the chronic degenerative changes. The pathogenesis of joint degeneration in hemochromatosis is not well understood and may involve iron inhibition of pyrophosphatase in cartilage; synovial biopsies have revealed ferritin and hemosiderin deposits in synovial cells in addition to calcium pyrophosphate dihydrate (CPPD) crystals. Treatment of hemochromatosis is with phlebotomy, but the arthropathy does not improve with iron removal. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used for analgesic treatment of arthropathy.

Neuropathic Arthropathy (Charcot Joint)

Neuropathic arthropathy (Charcot joint) is a progressive joint destruction, usually monarticular, accompanied by sensory loss. It commonly affects patients with diabetic neuropathy. Less common causes are familial peripheral neuropathy, tabes dorsalis, amyloidosis, cervical syringomyelia, and leprosy. The sites of joint involvement depend on the distribution of the underlying disorder but are typically the ankle and midfoot. Patients with diabetic neuropathic arthropathy have had diabetes for an average of 10 years. Frequently, the diabetes is poorly controlled. Diabetic peripheral neuropathy causes blunted pain perception and poor proprioception. The pathogenesis is poorly understood but is believed to be related to repeated microtrauma, overt trauma, small vessel occlusive disease (diabetes), and neuropathic dystrophic effects on bone.

The clinical features of neuropathic arthropathy are distinct. Patients may present with edema, erythema, and warmth of the affected joint, but the pain symptoms often appear mild because of a sensory deficit. Major structural changes occur, involving collapse of the tarsal bones resulting in a convexity of the plantar surface (rocker-bottom foot). Callus formation occurs over the weight-bearing site of bony damage, and the callus may blister and ulcerate. Infection can spread from skin ulcers to the bone. Osteomyelitis frequently complicates diabetic neuropathic arthropathy and should be suspected when an affected patient with diabetes has sudden worsening of glucose control.

Neuropathic arthropathy can be readily diagnosed with plain radiography. Yet in the early stages, the joint may look normal, or swelling of soft tissues or a small joint effusion may be present. In the later stages, radiography shows a disorganized joint architecture with presence of severe joint destruction, bony debris, and simultaneous features of bone resorption and new bone formation. Bone fractures may be seen as free bodies in the joint space; coalescence of bone fragments may then form characteristic sclerotic loose bodies. Progression of a neuropathic joint is rapid and may occur within a few weeks, possibly owing to microfractures that lead to considerable bone fragmentation and destruction.

No curative treatment is available for neuropathic arthropathy, but early diagnosis is central to preventing progressive joint destruction. Good local foot care, treatment of secondary infections, and protected weight bearing are important elements of conservative management. Immobilization of the joint with a brace and rest should be done in the early stages to stabilize the joint. Specialist care is necessary.

Osteonecrosis

Osteonecrosis is bone death related to loss of blood supply and may lead to collapse of the articular cartilage surface—and to secondary osteoarthritis. The most common location for osteonecrosis is the femoral head, but it also occurs in the distal femur, humeral head, and bones of the wrist, foot, and ankle. Osteonecrosis occurs more frequently for men than women (ratio, approximately 8:1). Trauma such as a femoral neck fracture that interrupts the blood supply to the femoral head is a common cause of osteonecrosis. Many nontraumatic causes exist, and the mechanism of vascular and bone injury continues to be obscure. Common causes are systemic glucosteroid therapy, alcohol abuse, sickle cell disease, connective tissue diseases such as systemic lupus erythematosus, and antiphospholipid antibodies (Box 82.1). No underlying cause can be identified in 10% to 25% of cases. Clinical characteristics depend on the location of osteonecrosis but are commonly seen with the sudden onset of activity and weight-bearing–localized joint pain.

KEY FACTS

- ✓ Osteoarthritis causes 2 principal changes—progressive focal degeneration of articular cartilage and formation of osteophytes
- ✓ The arthropathy of hemochromatosis affects second and third metacarpophalangeals and large joints not typically involved in primary osteoarthritis
- ✓ Neuropathic arthropathy—may present with a joint that is swollen, red, and warm but only mildly painful (sensory deficit)
- ✓ Osteonecrosis most commonly occurs in the femoral head and less commonly in the distal femur, humeral head, wrist, foot, and ankle

Early diagnosis of osteonecrosis depends on the clinician's index of suspicion, because plain radiographs often show no

Box 82.1 • Mnemonic ASEPTIC for Causes of Aseptic Necrosis of Bone

A	Alcohol, atherosclerotic vascular disease
S	Steroids[a], sickle cell anemia, storage disease (Gaucher disease)
E	Emboli (eg, fat, cholesterol)
P	Postradiation necrosis
T	Trauma
I	Idiopathic
C	Connective tissue disease (especially SLE), caisson disease

Abbreviation: SLE, systemic lupus erythematosus.

[a] Corticosteroids.

abnormalities in the early stages. Early radiographic changes may involve joint osteopenia with a central area of radiolucency with a sclerotic border; subchondral radiolucency, the so-called crescent sign, may occur, indicating a subchondral fracture. Magnetic resonance imaging (MRI) is the preferred imaging technique for the diagnosis of preradiographic osteonecrosis.

Treatment is generally conservative and involves reduced weight bearing and analgesics. Progressive bone collapse and pain are treated with joint arthroplasty.

Hemophilic Arthropathy

Hemophilic arthropathy, a form of secondary osteoarthritis, is related to recurrent hemarthroses of patients with hemophilia. The most commonly involved joints are the ankle, knee, and elbow. Bleeding may be provoked by trauma or occur spontaneously. Acute episodes are manifested by a painful monoarthritis with a bloody effusion. They are managed with aspiration, analgesia, joint rest, and clotting factor replacement. Over time, recurrent bleeding leads to synovial hemosiderin deposition, synovitis, and joint destruction. Patients with hemophilia and recurrent acute hemarthroses manifested by severe swelling and pain are at risk for hemophilic arthropathy. Specific radiographic abnormalities found in hemophilic arthropathy include widening of the intercondylar notch of the humeral and femoral areas. Management generally involves treatment of the underlying hemophilia and analgesia.

Radiographic Features

The radiographic features of osteoarthritis do not always predict the extent of symptoms. When radiographs are obtained, weight-bearing images should be included to appreciate the degree of joint space loss. Plain radiographs are insensitive for very early disease, and in selected circumstances, MRI may be needed. However, osteoarthritis is most commonly diagnosed clinically, and extensive imaging is frequently not necessary for its management. With aging, radiographic osteoarthritis is far more prevalent than the clinical illness. Radiographic features include osteophyte formation, asymmetrical joint-space narrowing, subchondral bony sclerosis, and subchondral cysts. The later bony changes include malalignment and deformity (Figure 82.2). In the spine, the radiographic finding called *spondylosis* includes anterolateral spinous osteophytes and degenerative disk disease with disk-space narrowing.

No laboratory test is useful for diagnosis of osteoarthritis. Evaluation of a painful effusion in an osteoarthritic joint is indicated to exclude an alternative diagnosis, most commonly crystalline arthritis.

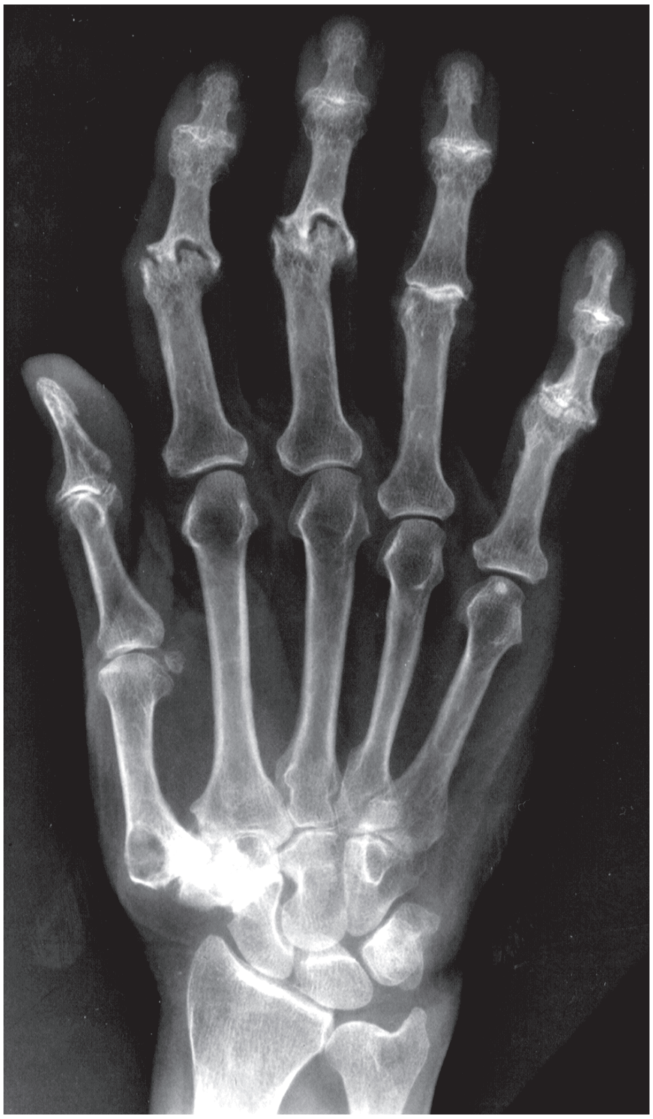

Figure 82.2. *Severe Osteoarthritis. Hypertrophic changes, asymmetrical joint-space narrowing, and subchondral sclerosis are prominent at the interphalangeal joints and at the first carpometacarpal joint. Of note, the metacarpophalangeal joints are completely spared, distinguishing this arthritis from rheumatoid arthritis. Additionally, joint-space narrowing and sclerosis are apparent at the base of the thumb at the first carpometacarpal joint and between the trapezium and the scaphoid. Osteoarthritis does not affect the entire wrist compartment equally. The involvement seen here is the most common. An additional interesting characteristic is central erosions at the second and third proximal interphalangeal joints. This variant occasionally has been called* erosive osteoarthritis.

Therapy

Therapeutic goals include pain relief, joint motion and function preservation, and prevention of further injury and wear of cartilage. Addressing the patient's ability to cope with the illness may be more helpful than medication therapy alone. Discussion about prognosis and reassurance regarding the absence of rheumatoid arthritis are important. Weight loss (especially in knee osteoarthritis), use of canes or crutches, correction of postural abnormalities, and proper shoe support are important measures. Splinting is helpful for symptomatic carpometacarpal thumb disease. Isometric or isotonic range-of-motion exercise, muscle strengthening, and overall aerobic fitness provide the para-articular structures with extra support and help reduce symptoms. Relief of muscle spasm with local application of heat or cold to decrease pain can help.

Initial drug therapy should be analgesics, such as acetaminophen. NSAIDs are beneficial for patients with inadequate response to acetaminophen. The NSAIDs ideally are used only as needed and at the lowest dose possible, which should be emphasized to the patient. Proton pump inhibitors should be prescribed for patients at risk for NSAID gastropathy and bleeding. Topical diclofenac or capsaicin may be helpful for patients with hand or knee osteoarthritis and should be considered before systemic NSAID therapy. Selective use of opioid analgesics can be considered for disabling pain, especially for patients who are not surgical candidates. Intra-articular corticosteroids offer temporary relief for joint flare-ups. Hyaluronic acid injections have minimal symptomatic benefit for selected patients with osteoarthritis of the knee. Supplements such as chondroitin and glucosamine sulfate are of no proven benefit.

Joint arthroplasty relieves pain, stabilizes joints, and improves function. Total joint arthroplasty is successful at the knee, shoulder, and hip. Box 82.2 describes the indications for total joint arthroplasty. When patients have established osteoarthritis of the knee, arthroscopic débridement procedures have no lasting benefit. This surgical procedure is no longer recommended. Herniated disks or spinal stenosis with radicular symptoms may require decompression.

Crystalline Arthropathic Disease

Hyperuricemia and Gout

Hyperuricemia occurs in 2% to 18% of healthy populations. It is associated with hypertension, renal insufficiency, obesity, and arteriosclerotic heart disease. Clinical gouty arthritis ranges in prevalence from 0.1% to 0.4%; it is the most common form of inflammatory arthritis in men. Among patients with gouty arthritis, 20% have a family history of gout. Because of the rising rates of obesity and metabolic syndrome, gout is becoming even more prevalent. Patients are typically hyperuricemic for years before their first episode of acute gout. Among patients with gout, 90% have reduced renal clearance of urate. Several abnormalities of renal tubular transport sites have been identified as the cause of urate underexcretion. Estrogen is uricosuric and is the mechanism for the rarity of gout in premenopausal women.

Box 82.2 • Indications for Total Joint Arthroplasty

- Radiographically advanced osteoarthritis
- Night pain that cannot be modified by changing position
- Lockup or giving way of the weight-bearing joint, associated with falls or near falls
- Joint symptoms that compromise activities of daily living

Box 82.3 • Causes of Secondary Hyperuricemia

- Overproduction of uric acid
  - Myeloproliferative disorders
    - Polycythemia, primary or secondary
    - Myeloid metaplasia
    - Chronic myelocytic leukemia
  - Lymphoproliferative disorders
    - Chronic lymphocytic leukemia
  - Plasma cell proliferative disorders
    - Multiple myeloma
  - Disseminated carcinoma and sarcoma
  - Sickle cell anemia, thalassemia, and other forms of chronic hemolytic anemia
  - Psoriasis
  - Cytotoxic drugs
  - Infectious mononucleosis
  - Obesity
  - Increased purine ingestion
- Underexcretion of uric acid
  - Intrinsic renal disease
    - Chronic renal insufficiency of diverse cause
    - Saturnine gout (lead nephropathy)
  - Drug-induced
    - Thiazide diuretics, furosemide, ethacrynic acid, ethambutol, pyrazinamide, low-dose aspirin, cyclosporine, nicotinic acid, laxative abuse, levodopa, rasburicase
  - Endocrine conditions
    - Adrenal insufficiency, nephrogenic diabetes insipidus, hyperparathyroidism, hypoparathyroidism, pseudohypoparathyroidism, hypothyroidism
  - Metabolic conditions
    - Diabetic ketoacidosis, lactic acidosis, starvation, ethanol abuse, glycogen storage disease type I, Bartter syndrome
  - Other
    - Sarcoidosis
    - Down syndrome
    - Beryllium disease

Causes of Secondary Hyperuricemia

Secondary hyperuricemia can be attributed to overproduction or underexcretion of uric acid (Box 82.3). Important causes of overproduction of uric acid include alcohol consumption, cancer, psoriasis, and sickle cell anemia. Excessive dietary purine intake is a common cause of overproduction. Important causes of underexcretion of uric acid include chronic renal insufficiency, lead nephropathy, diabetic ketoacidosis, and drugs, notably thiazide diuretics, nicotinic acid, low-dose aspirin, and calcineurin inhibitors.

Factors Predisposing to Acute Gout

Factors that precipitate gout include ketosis related to fasting, trauma, surgery, dietary indiscretions, and use of alcohol, especially beer.

Clinical Manifestations of Acute Gout

In most patients with gout, the metatarsophalangeal joint of the great toe is involved initially (podagra). Rapid joint swelling is associated with intense pain and extreme tenderness. Symptoms in the foot often awaken the person in the early morning. The attack may last for 2 weeks or more. Immediate treatment shortens the episode duration. Urate crystals, which are needle shaped and appear strongly negatively birefringent under polarized light, are found in the joint during an acute attack. The diagnosis of gout is established by the demonstration of monosodium urate crystals in the joint aspirate. Empirical treatment of gout may be needed when historical features of podagra are present but urate crystals cannot be shown with synovial fluid analysis.

Gout occurs most commonly in middle-aged men, but after menopause, women have an increased prevalence of gout. Although gout is usually monoarticular and regularly involves the joints in the lower extremity, attacks may become polyarticular over time. Bursae, such as those at the olecranon, may also be involved. For elderly patients taking diuretics, the first episode of gout may appear in an osteoarthritic hand.

KEY FACTS

- ✓ Nine of 10 patients with gout have reduced renal clearance of urate
- ✓ Gout initially involves the metatarsophalangeal joint of the great toe (podagra) in most patients
- ✓ Finding urate crystals (needle-shaped and strongly negatively birefringent under polarized light) in joint aspirate during an acute attack establishes the diagnosis of gout
- ✓ Gout may eventually involve multiple joints and also bursae

Treatment of Acute Gouty Arthritis

NSAIDs, such as indomethacin or naproxen, are the drugs of choice for treatment of acute gouty arthritis and should be used in a 7- to 10-day course. These drugs are contraindicated for patients with aspirin hypersensitivity, congestive heart failure, active peptic ulcer disease, or renal insufficiency. Glucocorticoids (oral, intramuscular, intravenous, or intra-articular) are the best choice for a patient who has contraindications to NSAIDs, is taking anticoagulants, or is hospitalized. A typical oral regimen is a moderate dose of corticosteroids, such as 20 or 30 mg of prednisone, daily for 5 days. This oral regimen may need to be repeated if gout recurs after its completion. Colchicine may be administered in the first 24 hours of an acute gout flare at a 1.2-mg dose, followed at 1 hour later with a 0.6-mg dose. Colchicine should not be given to transplant patients taking cyclosporine or to patients with liver or renal disease.

Treatment During an Intercritical Period

Oral colchicine, 0.6 mg twice daily, may be given prophylactically for up to 6 months when uric acid–lowering therapy is started to prevent exacerbation of acute gout. Long-term use of low-dose colchicine can be associated with a myopathy and neuropathy, especially for patients with renal insufficiency. A myoneuropathy may result for patients taking medications that affect colchicine metabolism through the cytochrome P450 system. These medications include cyclosporine, simvastatin, lovastatin, atorvastatin, diltiazem, cimetidine, verapamil, and amiodarone.

Treatment of Recurrent or Chronic Gout

Urate acid–lowering therapy with a xanthine oxidase inhibitor is indicated for persons with more than 2 gout attacks over the past 12 months or patients with soft-tissue tophi, gouty erosions seen on radiographs, or uric acid nephrolithiasis. The goal of therapy is to consistently maintain a serum uric acid level below 6 mg/dL, thus preventing new joint urate crystallization and resorption of the existing deposits. If the patient has severe tophaceous gout, then the goal serum uric acid level should be below 5 mg/dL.

KEY FACTS

- ✓ Colchicine, 1.2 mg as a single dose followed in 1 hour by a 0.6-mg dose, is a therapeutic option for acute gouty arthritis
- ✓ Indications for uric acid–lowering therapy—more than 2 gout attacks in the past year, or soft-tissue tophi, gouty erosions on radiographs, or uric acid nephrolithiasis
- ✓ Therapeutic goal for gout—the serum uric acid level kept below 6 mg/dL to prevent new and reduce existing urate deposits

The uricosuric agent probenecid inhibits tubular reabsorption of filtered and secreted urate. Probenecid should not be used if the patient has a creatinine clearance less than 50 mL/min or a history of kidney stones. This drug requires twice-daily use and has generally been replaced by once-daily xanthine oxidase inhibitors.

Allopurinol is the standard xanthine oxidase inhibitor. Its use should not be started during an acute gout attack. Allopurinol can cause a rare hypersensitivity syndrome: eosinophilia, fever, hepatitis, renal failure, and erythematous desquamative rash. This syndrome is observed most commonly in patients with renal insufficiency and in persons with Southeast Asian ethnicity (persons of Korean, Chinese, or Thai descent) who have the genetic marker HLA-B*5801. Before initiation of allopurinol, HLA-B*5801 screening should be considered for these high-risk populations. Allopurinol may be used for patients with renal insufficiency. One suggested guideline for the starting dose is 1.5 times the estimated glomerular filtration rate. The dose of allopurinol is then gradually increased by 50-mg increments until the target serum uric acid level has been reached. Many patients with normal renal function may need more than 300 mg of allopurinol daily to reach an appropriate uric acid level. Febuxostat is a xanthine oxidase inhibitor that can be used for patients who are allergic to allopurinol. Both febuxostat and allopurinol interfere with the metabolism of 6-mercaptopurine and azathioprine, thereby increasing the risk of bone marrow toxicity. Ideally, they should be avoided for persons who require xanthine oxidase inhibition. For transplant patients, azathioprine is replaced with mycophenolate mofetil when patients require allopurinol or febuxostat.

Pegloticase (pegylated uricase), which converts uric acid to allantoin, is approved for chronic gout that is refractory to conventional therapy. For patients with extensive tophaceous deposits, it promotes more rapid resolution. Pegloticase administered intravenously is a short-term therapy because inactivating antibodies can develop.

Lesinurad is a urate transporter inhibitor newly approved by the US Food and Drug Administration for treatment of gout for patients who have an inadequate response to xanthine oxidase inhibitors. Lesinurad is added to allopurinol or febuxostat to improve hyperuricemia. It should not be used for patients with renal insufficiency.

Box 82.4 lists important points to remember in the management of gout.

Box 82.4 • Important Points in Gout Management

Treatment of hyperuricemia may slow the decline of the glomerular filtration rate in patients with chronic kidney disease.

Most rheumatologists do not treat asymptomatic hyperuricemia. In the future, this may change for persons with myocardial failure, coronary artery disease, or chronic kidney disease.

Gout and hyperuricemia cannot be treated exclusively with dietary modification. However, patients should be advised to avoid red meat, seafood, beer, and concentrated fructose because these foods may trigger an attack. Dairy proteins, vitamin C, and coffee help to lower the serum uric acid level. Both losartan and fenofibrate have mild uricosuric effects and can be helpful in hyperuricemic patients, with appropriate indications for their use. Weight loss helps to reduce the frequency of acute gout.

Up to 33% of patients with acute gout have a normal serum uric acid level at the time of the acute attack. A serum uric acid determination is not recommended for the evaluation of acute gout. This should be obtained after the attack has remitted.

One-half of synovial fluid samples aspirated from first metatarsophalangeal or other previously involved joints of asymptomatic patients with gout have crystals of monosodium urate.

Gout in a premenopausal woman is unusual.

A septic joint can trigger an attack of gout or pseudogout in a predisposed person. Synovial fluid should always be analyzed for crystals and subjected to Gram stain and culture.

The frequency of gout in patients who have had an organ transplant is high (25%). (Both calcineurin inhibitors and diuretics cause hyperuricemia.)

CPPD Disease

Classification

CPPD disease has 3 main categories: hereditary or familial (eg, Slovakian, Dutch, or Canadian ancestry), secondary, and sporadic. Diseases associated with CPPD include metabolic disorders such as hyperparathyroidism (strong association), hemochromatosis (strong association), hypophosphatasia, hypomagnesemia, and familial hypocalciuric hypercalcemia.

Clinical Features

The main clinical presentations of CPPD disease are acute synovitis and chronic arthropathy. Radiographic evidence of chondrocalcinosis, such as calcifications in hyaline cartilage of the knee and triangular fibrocartilage complex of the wrist, is often an incidental finding among elderly persons. The release of CPPD crystals can induce an acute inflammatory arthritis called **pseudogout**. Most commonly, pseudogout affects knees and wrists, but shoulders, elbows, ankles, and intervertebral disks also can be affected. Pseudogout rarely affects more than 1 joint during an attack, except among hospitalized elderly patients. Acute attacks are self-limiting, generally lasting 1 week. Fever and delirium may occur in elderly persons. Chronic CPPD arthropathy is a structural abnormality of cartilage with osteophyte and cyst formation and CPPD crystal deposition within the joint; superimposed pseudogout attacks may occur. The joints most commonly affected are the knees and wrists, followed by the shoulders, hips, metacarpophalangeal joints, and metatarsophalangeal joints. Patients may present with chronic pain and stiffness with limitation of function of the affected joints, which may be misdiagnosed as rheumatoid arthritis.

Key Definition

Pseudogout: *an inflammatory arthritis resulting from the formation of calcium pyrophosphate dihydrate crystals in articular and hyaline cartilage and fibrocartilage.*

Pathogenesis

The formation of CPPD crystals may be related to effects on the metabolism of inorganic pyrophosphate present in synovial fluid. Local joint factors that may influence CPPD crystal formation include absence of magnesium, excessive calcium, and absence of alkaline phosphatase within synovial fluid and tissue. CPPD crystals stimulate inflammation through a mechanism related to elaboration of proinflammatory cytokines, similar to that in acute gout; the acute inflammatory reaction is often precipitated by trauma.

Diagnosis

For definitive diagnosis, CPPD crystals must be identified in joint fluid obtained by arthrocentesis, CPPD crystals show weakly positive birefringence under compensated polarized light microscopy. The presence of characteristic calcifications along the hyaline cartilage and fibrocartilage on plain radiographs supports a CPPD disease diagnosis; however, the acute synovitis of pseudogout may be seen in patients without visible chondrocalcinosis.

Treatment

Unlike for gout, there is no treatment that prevents the formation or promotes the elimination of CPPD crystals. If an underlying metabolic disorder associated with CPPD such as hyperparathyroidism is present, it should be recognized and treated. For treatment of attacks of pseudogout, NSAIDs, oral prednisone, or an intra-articular injection of a glucocorticoid preparation into the swollen joint can be effective. Low-dose oral colchicine may lead to a decrease in the frequency and severity of attacks, but adverse effects may preclude its prolonged use. Chondrocalcinosis is asymptomatic and therefore is not treated.

KEY FACTS

- ✓ Diseases associated with CPPD—hyperparathyroidism (strong association), hemochromatosis (strong association), hypophosphatasia, hypomagnesemia, and familial hypocalciuric hypercalcemia
- ✓ Observation of CPPD crystals (weakly positively birefringent under polarized light) in joint aspirate is needed for a definitive diagnosis of CPPD disease
- ✓ Characteristic chondrocalcinosis on plain radiographs supports a CPPD disease diagnosis but may be absent in pseudogout
- ✓ Therapies for pseudogout—include NSAIDs, oral corticosteroids, and intra-articular corticosteroid injection; adverse effects may limit use of low-dose oral colchicine

Basic Calcium Phosphate Deposition Disease

Presentation

The main clinical presentations of basic calcium phosphate disease are acute inflammation, such as calcific tendinitis, bursitis, or periarthritis, and chronic articular inflammation, including Milwaukee shoulder, a noninflammatory pastelike joint fluid containing hydroxyapatite. Subcutaneous deposits of basic calcium phosphate may be found in the tissues of patients with scleroderma or dermatomyositis, particularly juvenile dermatomyositis (calcinosis cutis).

Diagnosis and Treatment

Diagnosis of basic calcium phosphate disease may be difficult. Individual crystals are not birefringent, so they cannot be seen on routine polarized light microscopy (Table 82.2). Treatment involves NSAIDs and intra-articular corticosteroid injections. Subcutaneous basic calcium phosphate disease is difficult to treat. Recently, topical, intralesional, and intravenous sodium thiosulfate has been used with mild success, possibly related to the dissolution of calcium salts.

Calcium Oxalate Arthropathy

Calcium oxalate arthropathy occurs in patients with primary oxalosis and patients with renal failure—usually those undergoing long-term hemodialysis. It can cause acute inflammatory arthritis. Crystals are large, bipyramidal, envelope-shaped, and strongly birefringent. Calcium oxalate can cause calcification of articular structures that is apparent on radiographs.

Other Crystalline Arthropathies

Several other types of crystals have been identified in soft tissues, bursa, and joints. Cholesterol crystals have been found in the synovial fluid or olecranon bursa, or both, of patients with rheumatoid arthritis and other inflammatory arthritides. The crystals look like broad squares with a notched corner. Corticosteroid crystals have been found after an intra-articular corticosteroid injection; they can induce an inflammatory reaction and synovitis manifested by a painful swollen joint within 8 hours after injection. Aspiration is often done to exclude infection. The diagnosis of corticosteroid crystalline arthropathy may be supported by the presence of irregular square and rod-shaped crystals. Corticosteroid crystals often have been phagocytosed by neutrophils and macrophages. Charcot-Leyden crystals have been found in hypereosinophilic syndromes; these crystals have a spindle-shaped appearance and are weakly birefringent.

Idiopathic Inflammatory Myopathies

The **idiopathic inflammatory myopathies** are a group of rare systemic inflammatory muscle diseases categorized into 3 main

Table 82.2 • Differential Diagnosis of Basic Calcium Phosphate Disease According to Results of Synovial Fluid Analysis

Diagnosis	Leukocyte Count, $\times 10^9$/L	Differential	Polarization Microscopy
Degenerative joint disease	<1	Mononuclear cells	Negative
Rheumatoid arthritis	5-50	PMNs	Negative
Gout	5-100	PMNs	Monosodium urate
Pseudogout	5-100	PMNs	CPPD disease
Hydroxyapatite	5-100	PMNs	Negative
Septic arthritis	≥100	PMNs	Negative

Abbreviations: CPPD, calcium pyrophosphate dihydrate; PMN, polymorphonuclear leukocyte.

subtypes: dermatomyositis, polymyositis, and sporadic inclusion body myositis. They have distinct clinical features and histopathologic abnormalities on muscle biopsies characterized by inflammatory infiltrates composed primarily of T cells, B cells, plasmacytoid dendritic cells, and macrophages. Patients with idiopathic inflammatory myopathies have progressive muscle weakness, usually symmetrical, caused by muscle inflammation and extramuscular organ involvement. Dermatomyositis affects persons in a bimodal distribution, with onset in the age range of 16 years or younger (called *juvenile dermatomyositis*) and in the mid-40s to 50s. Inclusion body myositis occurs in persons older than 50 years and affects men more often than women (3:1 ratio). Other types of inflammatory myopathies are cancer-associated myositis and connective tissue disease–associated myositis, seen in patients with scleroderma, mixed connective tissue disease, Sjögren syndrome, and systemic lupus erythematosus. Cancer-associated myositis is considered a paraneoplastic syndrome triggered by a malignant tumor, typically breast, ovarian, lung, or prostate, in persons older than 50 years.

Key Definition

Idiopathic inflammatory myopathies: *a group of rare systemic inflammatory muscle diseases categorized into 3 main subtypes: dermatomyositis, polymyositis, and inclusion body myositis.*

Clinical Features

Dermatomyositis presents with symmetrical proximal muscle weakness and several classic photosensitive rashes (Box 82.5). Nailfold capillary abnormalities usually occur and can be visualized with an ophthalmoscope as dilated, enlarged capillary loops that are disorganized with capillary loss. Although more common for persons with juvenile dermatomyositis, calcinosis may occur over the extensor surfaces, such as elbows and knees. Extramuscular organ involvement may develop in the pulmonary, gastrointestinal tract, and cardiac systems.

Amyopathic dermatomyositis is a subtype of dermatomyositis with characteristic photosensitive rashes as seen in dermatomyositis but with minimal or no muscle involvement. These patients generally have a less aggressive course than those with dermatomyositis, although a malignancy may be present at diagnosis in approximately 10% of patients. A rare subset of patients with amyopathic dermatomyositis has rapidly progressive interstitial pneumonia. They may have a myositis-specific antibody called the *MDA-5* (melanoma differentiation gene 5) antibody.

Polymyositis also is characterized by symmetrical proximal muscle weakness but without the rashes seen in dermatomyositis. As in dermatomyositis, other organs may be affected by inflammation or skeletal muscle weakness, or both. For example, interstitial lung disease may occur, typically as nonspecific interstitial pneumonia or progressive respiratory muscle weakness leading to respiratory failure. In the gastrointestinal tract system, dysphagia from weakness of the cricopharyngeal muscle may be prominent and result in aspiration pneumonia; in the cardiac system, arrhythmias or myocarditis may occur.

A subset of patients with dermatomyositis or polymyositis have features characteristic of antisynthetase syndrome. These patients present with fever; Raynaud phenomenon; arthritis; so-called mechanic's hands due to hyperkeratosis of the lateral aspects of the finger pads, primarily in the second and

Box 82.5 • Rashes of Dermatomyositis

Heliotrope rash of the eyelids with periorbital edema

Erythematous papular rash on metacarpophalangeal and proximal interphalangeal joints (Gottron papules)

Erythematous scaly rash over extensor surfaces of metacarpophalangeals, proximal interphalangeals, elbows, and knees (Gottron sign)

V sign of the chest

Shawl sign affecting the upper back and neck

Patchy erythema of the face

third digits; and interstitial lung disease that may be progressive and refractory to treatment with corticosteroids and other immunosuppressives. Eight antibodies against the aminoacyl-transfer RNA synthetases have been discovered. Anti-Jo-1 antibodies have been commonly reported with a prevalence of 20% to 40%, but other, rarer (<1%-5% prevalence) autoantibodies exist, such as anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-Ks, anti-Ha, and anti-Zo antibodies.

The characteristic features of sporadic inclusion body myositis are insidious onset of weakness with proximal and distal muscle involvement, such as the finger flexors and wrist muscles. Some patients may have asymmetrical muscle involvement. Severe muscle atrophy of the forearm compartment muscles or quadriceps, or both, may be seen. Patients often present after frequent falls of unknown cause. Dysphagia is also a prominent symptom and may progress to require feeding tube placement.

Diagnosis

The workup for patients suspected of having an idiopathic inflammatory myopathy involves several testing modalities. Serum levels are measured for the muscle enzymes creatine kinase, aldolase, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase. Creatine kinase measurement is the most sensitive and accurate laboratory test reflecting muscle inflammation, but its sensitivity diminishes as the muscle disease becomes chronic and muscle inflammation gives way to fibrosis and scarring. In inclusion body myositis, creatine kinase values may be minimally increased or normal at presentation. Electromyography of patients with dermatomyositis or polymyositis characteristically shows polyphasic motor unit potentials with decreased amplitudes, increased spike frequency, and fibrillation potentials that indicate active disease. MRI studies of affected muscle groups have been gaining use as a noninvasive means of detecting muscle inflammation. A muscle biopsy must be obtained on the contralateral side from where electromyography was performed, and preferably the muscle sample is obtained from an area that showed weakness on examination.

Muscle biopsies are the gold standard for confirming the diagnosis of idiopathic inflammatory myopathy. They characteristically show degeneration, necrosis, and regeneration of myofibrils with a lymphocytic inflammatory infiltrate. The pathogenesis of dermatomyositis and juvenile dermatomyositis involves deposition of C5b-C9 membrane attack complex and complement in the muscle microvasculature, leading to tissue hypoperfusion and fiber atrophy. In dermatomyositis and juvenile dermatomyositis, CD4 T cells, B cells, and plasmacytoid dendritic cells are found in the perivascular and perimysial areas, invading nonnecrotic muscle fibers that express major histocompatibility complex class I. In polymyositis and inclusion body myositis, CD8 cytotoxic T cells are located within the endomysium; they surround and invade nonnecrotic muscle fibers that express major histocompatibility complex class I, leading to fiber necrosis and regeneration. In inclusion body myositis, characteristic features are degenerative proteins that accumulate in muscle tissue; rimmed vacuoles, congophilic amyloid deposits, and 15- to 18-nm tubulofilament inclusions, seen on electron microscopy of the muscle biopsy specimen.

KEY FACTS

✓ Classic rashes associated with dermatomyositis—heliotrope rash, Gottron papules, Gottron sign, *V* sign of the chest, shawl sign on the upper back and neck, and facial dermatitis

✓ Polymyositis and dermatomyositis—both involve symmetrical proximal muscle weakness, but only dermatomyositis has characteristic rashes

✓ Characteristic features of inclusion body myositis—insidious onset of weakness with proximal and distal muscle involvement (eg, in finger flexors and wrist muscles)

✓ For confirmation of idiopathic inflammatory myopathy—muscle biopsy continues to be the gold standard

Autoantibodies against nuclear and cytoplasmic antigens are frequently seen in idiopathic inflammatory myopathies. The myositis-specific autoantibodies are useful in the definition of specific myositis subsets. In addition to the antibodies against the aminoacyl-transfer RNA synthetases that define the antisynthetase syndrome, other myositis-specific antibodies include anti-Mi-2, anti-SRP, and anti-MDA-5. They are present in approximately 5% to 20% of patients with idiopathic inflammatory myopathies. The anti-Mi-2 antibody is directed against the nuclear helicase protein, Mi-2; it is associated with classic dermatomyositis rashes and a milder myositis course. The anti-SRP antibody is directed against the signal recognition particle; it is associated with severe necrotizing myopathy, cardiomyopathy, and a poor prognosis. The anti-MDA-5 antibody is an RNA helicase first described in persons of Asian descent who had amyopathic dermatomyositis; it is associated with rapidly progressive interstitial lung disease and a poor prognosis. Myositis-associated autoantibodies, such as the anti-PM-Scl antibody, have been described in forms of myositis that overlap with scleroderma. The autoantibody cytosolic 5′-nucleotidase 1A (anti-cN-1A) may be seen in some patients with sporadic inclusion body myositis and may be predictive of serious bulbar, motor, and respiratory involvement.

An association has been well described between malignancy and the onset of idiopathic inflammatory myopathy. Occult malignancy may be present in up to 25% of patients with dermatomyositis and 10% to 15% of patients with polymyositis within 1 to 3 years of diagnosis. The described cancers have included breast, ovarian, colorectal, lung, endometrial, and renal cell carcinoma; nasopharyngeal carcinoma; prostate, urothelial, thyroid, neuroendocrine, and thymic carcinoma; myelodysplastic syndrome; lymphoma; chronic lymphocytic leukemia; and Waldenström macroglobulinemia. The cause is not well understood but may involve a paraneoplastic phenomenon manifested by a cross-reaction of cytotoxic T cells against tumor antigens expressed by regenerating muscle fiber cells. The anti-p155/140 antibody is an anti–transcription intermediary factor, TIF1-γ, and has been reported as strongly predictive of cancer-associated myositis. The NXP-2 antibody (nuclear matrix protein) has been reported as predictive of cancer in patients with newly diagnosed dermatomyositis.

Screening for an occult malignancy is strongly recommended at the diagnosis of dermatomyositis or polymyositis, with age- and sex-appropriate testing and computed tomography scans of chest, abdomen, and pelvis or a whole-body positron emission tomography–computed tomography scan. An elevated CA-125 level at diagnosis of dermatomyositis has been strongly predictive of ovarian or primary peritoneal cancer in women.

Treatment

Treatment of idiopathic inflammatory myopathies generally involves high-dose corticosteroids, usually intravenous for 1 to 3 days initially and then oral corticosteroids, such as prednisone at 1 mg/kg of body weight, for approximately 4 weeks with tapering every 2 to 4 weeks. The degree and frequency of tapering depend on normalization of the serum muscle enzyme levels and improvement of strength, stamina, and extramuscular organ involvement. A corticosteroid-sparing medication, such as methotrexate, azathioprine, or intravenous immunoglobulin, or a combination, generally is started at the diagnosis of idiopathic inflammatory myopathy to allow for quicker tapering. For rashes associated with dermatomyositis, a topical corticosteroid, topical tacrolimus, hydroxychloroquine, and photoprotection with sunscreen are all generally effective. Patients with severe, refractory myositis or severe extramuscular involvement, such as progressive interstitial lung disease, may be treated with mycophenolate mofetil, cyclophosphamide, rituximab, or oral tacrolimus. To date, no immunosuppressive treatment is effective for inclusion body myositis. Intravenous immunoglobulin is commonly used for supportive treatment of progressive dysphagia in these patients.

KEY FACTS

- ✓ Malignancy is associated with idiopathic inflammatory myopathy; up to 25% of patients with dermatomyositis and 10% to 15% with polymyositis may have an occult malignancy within 1 to 3 years of diagnosis
- ✓ Idiopathic inflammatory myopathies—generally require high-dose corticosteroid therapy
- ✓ No effective immunosuppressive treatment is available for inclusion body myositis

Drug-Induced Myopathies

Drugs can cause an immune-mediated necrotizing myopathy. The drugs commonly implicated are the lipid-lowering drugs, such as statins, fibrates, and nicotinic acid. Other drugs associated with myopathies include corticosteroids, colchicine, chloroquine, hydroxychloroquine, zidovudine, D-penicillamine, ethanol, cocaine, and heroin. Patients who have a statin-induced myopathy may present with myalgias, increased creatine kinase levels, muscle weakness, and, rarely, rhabdomyolysis. The pathogenesis of statin-induced myopathy is not well understood, but it is related to an antibody-mediated immune mechanism, with elaboration of an autoantibody (anti-200/100 kDa protein) directed against hydroxymethylglutaryl-CoA reductase. Assays to detect the hydroxymethylglutaryl-CoA reductase antibody are commercially available and are useful to the diagnosis of statin-induced myopathy. A muscle biopsy does not show an inflammatory infiltrate; rather, T cells and macrophages surrounding necrotic and regenerating muscle fibers have been described.

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Rheumatoid Arthritis and Spondyloarthropathies

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Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by symmetrical synovitis, morning stiffness, and joint destruction. It affects 0.03% to 1.5% of the population worldwide. Women are affected 3 times more frequently than men. Its incidence peaks between the ages of 50 and 75 years. Lifetime risk of RA in adults is 3.6% for women and 1.7% for men. The presentation of an unknown antigen to a genetically susceptible person is believed to trigger RA. Recently, cigarette smoking has been identified as a risk factor for seropositive RA.

Key Definition

Rheumatoid arthritis: *a chronic systemic inflammatory disease characterized by joint destruction.*

Natural History

In most patients, the onset of rheumatoid arthritis is insidious, occurring over weeks to months. However, for one-third of patients, the onset is rapid and occurs over days or weeks. Early in the course of the disease, most patients have a predominantly small-joint (ie, hands, wrists, and forefeet) involvement. Spontaneous remission of RA almost never occurs after 2 years of disease. Patients who have a persistent polyarthritis with increased acute-phase reactants and a positive rheumatoid factor or anti–cyclic citrullinated peptide (CCP) antibody are at high risk for both early erosive disease within 1 to 2 years of symptom onset and early disability. The relationship between disease duration and inability to work is nearly linear. After 15 years of RA, 15% of patients are completely disabled. Life expectancy in severe seropositive RA is shortened, but it may be improving with the more aggressive early intervention available for the illness. Patients with RA are at increased risk for coronary artery disease, infections, and non-Hodgkin lymphoma.

Pathogenesis

RA development tends to occur in persons with a genetic predisposition who are exposed to certain environmental factors. This preclinical phase may occur for years before an inflammatory arthritis develops and can be diagnosed.

Genetic Predisposition

The strongest genetic link identified for the development of RA is the human leukocyte antigen (HLA)-DRB1 shared epitope. However, more than 100 non-HLA gene loci are implicated in RA susceptibility. Certain environmental factors have been found to interact with genes and increase RA susceptibility. Patients with HLA-DR4 who smoke cigarettes have a 20- to 40-fold increased susceptibility to RA. Other suspected environmental risks include periodontal disease and an altered gastrointestinal tract microbiome.

Preclinical Phase

Repeated activation of innate immunity in extra-articular tissues, especially at mucosal surfaces, appears to be the initiating

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insult in RA development. Citrullination (conversion of arginine to citrulline) or other posttranslational modification has been shown to occur. Peptidylarginine deiminase (PAD), an enzyme found in inflammatory tissues, facilitates citrullination. Smoking induces PAD expression in alveolar macrophages. *Porphyromonas gingivalis*, an oral anaerobe associated with periodontal disease, expresses PAD in the mouth. The gastrointestinal tract microbiome is likely another source for citrullination.

In RA, a breakdown occurs in the person's tolerance toward these citrullinated proteins, leading to production of anti–citrullinated protein antibodies (ACPAs). The antibodies are distinct to RA and can occur 3 to 7 years before the RA diagnosis. Epitope spreading (the development of antibodies against similar molecules) and increased cytokine production gradually increase the person's autoimmunity until RA disease becomes apparent.

Early RA

Microbial or mechanical insults have been proposed as damaging to the synovium. Vascular permeability also is increased, which allows the citrullinated self-antigens to travel into the synovium. The formation of immune complexes with the unknown antigen activates complement and, subsequently, the adaptive immune system. A single RA antigen is unlikely. Instead, a broad spectrum of modified citrullinated immune complexes present to autoreactive T and B lymphocytes, which stimulate proinflammatory cytokines such as tumor necrosis factor (TNF)-α (TNF-α), interleukin-6 (IL-6), and IL-1.

Established RA

After the inflammatory process is fully established, the synovium organizes itself into an invasive tissue called *pannus* that degrades cartilage and bone. The joint damage in RA is a consequence of both the innate and adaptive immune systems, fibroblastlike synoviocytes, and osteoclast activation. The fibroblastlike synoviocytes can migrate from joint to joint and thereby contribute to the symmetrical and diffuse distribution seen in RA.

Key Definition

Rheumatoid factor: *an immunoglobulin directed against the Fc portion of immunoglobulin G. It is detected in 70% to 80% of patients with rheumatoid arthritis.*

Clinical Features

Patients have joint swelling, pain, warmth, and stiffness with the onset of clinical disease. These symptoms and signs worsen as the synovial membrane proliferates and the inflammatory reaction increases. In studies of early arthritis, the histologic and radiographic evidence of rheumatoid synovitis is found in clinically unaffected joints, an indication that the disease is present before clinical manifestations appear. The joints most commonly involved in early RA (for more than 85% of patients) are the metacarpophalangeal, proximal interphalangeal, and wrist joints (Figure 83.1) and metatarsophalangeal joints. The distal interphalangeal joints are typically spared. The distribution of involvement is symmetrical and polyarticular (5 or more joints); small joints are involved predominantly. Ultimately, multiple other joints may be involved, including knees, ankles, elbows, shoulders, cricoarytenoid joints, and the cervical spine articulations. The joint enlargement feels spongy and occurs with the thickening of the synovium. An associated joint effusion may make the joint feel fluctuant. Patients describe deep aching and soreness in the involved joints—sensations that are aggravated with use and can be present at rest.

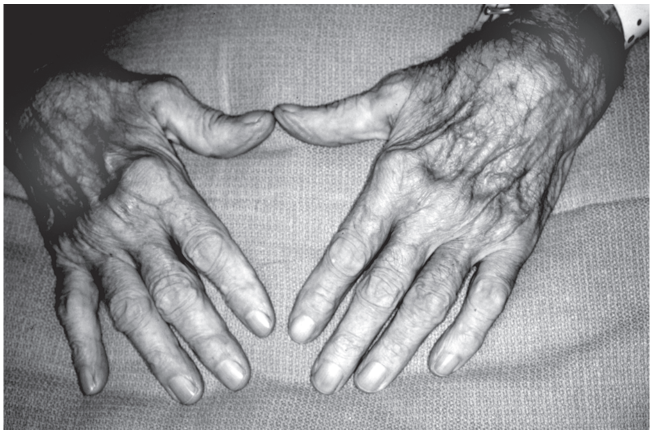


Figure 83.1. *Moderately Active Seropositive Rheumatoid Arthritis. The patient has soft tissue swelling across the entire row of proximal interphalangeal joints bilaterally and soft tissue swelling mounding up over the wrists. Of note, the lack of change at the distal interphalangeal joints is nearly complete.*

Constitutional Features

Morning stiffness of more than 1 hour, the so-called gelling phenomenon, throughout the body and recurrence of the stiffness after resting are 2 of the many constitutional characteristics that complicate RA. Fatigue, weight loss, muscle pain, excessive sweating, or low-grade fever may be reported by patients who present with RA. Adult seropositive RA is not a cause of fever of unknown origin because temperatures greater than 38.3°C cannot be attributed to the disease.

Musculoskeletal Complications

The musculoskeletal complications of RA include compression of the carpal bones, radial deviation at the carpus, and valgus of the ankle and foot (Box 83.1).

Cervical Spine

One-half of all patients with chronic RA have radiographic involvement of the atlantoaxial joint. This involvement is diagnosed from cervical flexion and extension radiographs that

Box 83.1 • Musculoskeletal Complications of Rheumatoid Arthritis

Characteristic deformities

Boutonnière deformity of the finger, with hyperextension of the distal interphalangeal joint and flexion of the proximal interphalangeal joint

Swan-neck deformity of the finger, with hyperextension at the proximal interphalangeal joint and flexion of the distal interphalangeal joint

Ulnar deviation of the metacarpophalangeal joints; can progress to complete volar subluxation of the proximal phalanx from the metacarpophalangeal head

Compression of the carpal bones and radial deviation at the carpus

Subluxation at the wrist

Valgus of the ankle and hindfoot

Pes planus

Forefoot varus and hallux valgus

Cock-up toes from subluxation at the metatarsophalangeal joints

show subluxation. Alternatively, some patients have subaxial subluxations, typically at 2 or more levels. The probability of cervical involvement is predicted by the severity and chronicity of peripheral arthritis. This rheumatoid complication has a high prevalence in patients with RA who are referred for orthopedic reconstructive surgery.

The cervical instability is usually asymptomatic; however, patients may have pain and stiffness in the neck and occipital region. Patients may present dramatically with drop attacks or tetraplegia, but more commonly, progression can be slow and subtle with symptoms of hand weakness or paresthesias or signs of cervical myelopathy. Interference with ischemic compression of blood flow through the anterior spinal artery or vertebral arteries (vertebrobasilar insufficiency) causes the neurologic symptoms. Erosive changes may promote basilar invagination of the odontoid process of C2 into the underside of the brain, causing spinal cord compression and death.

All patients with destructive RA should be treated with intubation precautions considered and with the assumption that cervical instability is present. New neurologic symptoms mandate an urgent neurologic evaluation, including magnetic resonance imaging (MRI) of the cervical spine and consideration of surgical intervention. Indications for surgical treatment include neurologic or vascular compromise and intractable pain. For active patients, prophylactic cervical spine stabilization is recommended when there is evidence of extreme (>8 mm) subluxation of C1 over C2.

Popliteal Cyst

Flexion of the knee markedly increases the intra-articular pressure of a swollen joint. This pressure produces an outpouching of the posterior components of the joint space, termed a *popliteal* or *Baker cyst*. Ultrasonographic examination of the popliteal space confirms the diagnosis. At dissection, the cyst can rupture into the calf, resembling acute thrombophlebitis and called *pseudothrombophlebitis*. Premature anticoagulation for possible phlebitis leads to a hematoma in the calf. Treatment of an acute cyst rupture includes bed rest, elevation of the leg, ice massage or cryocompression, and an intra-articular injection of corticosteroid therapy. Polpliteal cysts require medical management of the knee synovitis. Surgical resection is rarely recommended.

Tenosynovitis

Tenosynovitis is common in the finger flexor and extensor wrist tendon sheaths. Persistent inflammation can produce stenosing tenosynovitis, loss of function, and, ultimately, the rupture of tendons. Treatment of acute tenosynovitis includes immobilization, warm soaks, nonsteroidal anti-inflammatory drugs (NSAIDs), and local injections of corticosteroid in the tendon sheath.

Carpal Tunnel Syndrome

RA is a common cause of carpal tunnel syndrome. The sudden appearance of bilateral carpal tunnel syndrome should raise the question of an early inflammatory arthritis. This syndrome is associated with paresthesias of the hand in a typical median nerve distribution. Discomfort may radiate up the forearm or into the upper arm. The symptoms worsen with prolonged flexion of the wrist and at night. Late complications include thenar muscle weakness and atrophy and permanent sensory loss. Treatment includes resting splints, control of inflammation, and local injection of glucocorticosteroid. Surgical release is recommended for persistent symptoms.

KEY FACTS

✓ Anti-CCP antibodies—detected in most patients with seropositive RA; unlike rheumatoid factor, they are specific for RA

✓ Presentation of RA—a symmetrical, small joint (wrist, metacarpophalangeal, proximal interphalangeal, and metatarsophalangeal) polyarthritis lasting for more than 6 weeks

✓ The presence of a positive CCP antibody—increases the likelihood of early RA

✓ Constitutional features complicating RA—morning stiffness of more than 1 hour, gelling throughout the body, and recurrence of stiffness after resting

✓ One-half of all patients with RA have radiographic involvement of the atlantoaxial joint; the RA is diagnosed from cervical flexion and extension radiographs showing subluxation

Extra-articular Complications

Extra-articular complications of RA occur almost exclusively in patients who have high titers of rheumatoid factor and positive ACPA. In general, the number and severity of the extra-articular characteristics vary with the duration and severity of disease. Many classic extra-articular manifestations of RA have become less common with the advent of more aggressive treatment of early disease.

Rheumatoid Nodules

Rheumatoid nodules are the most common extra-articular manifestation of seropositive RA. More than 20% of patients have rheumatoid nodules, which occur over extensor surfaces and at pressure points. Rarely, they occur in the lungs, heart, sclera, and dura mater. The nodules have characteristic histopathologic features. A collagenous capsule and a perivascular collection of chronic inflammatory cells surround a central area of necrosis encircled by palisading fibroblasts. Breakdown of the skin over rheumatoid nodules, resulting in ulcers and infection, can be a major source of morbidity. The infection can spread to local bursae, infect bone, or spread hematogenously to joints.

Rheumatoid Vasculitis

Rheumatoid vasculitis usually occurs in persons with severe, deforming arthritis and a high titer of rheumatoid factor. It is rarely encountered today, since the advent of more aggressive RA therapies. As an immune complex vasculitis, it may present as palpable purpura, mononeuritis multiplex, or a medium-vessel polyarteritis–like syndrome affecting visceral organs.

Neurologic Manifestations

The most common neurologic complication of RA is carpal tunnel syndrome. For patients with advanced joint disease, cervical vertebral subluxation can cause myelopathy, and therefore preoperative cervical spine radiographs in flexion and extension views should be considered.

Pulmonary Manifestations

Pleural disease has been noted in more than 40% of autopsies of persons with RA, but clinically important pleural disease is less frequent. Characteristically, rheumatoid pleural effusions are asymptomatic until they become large enough to interfere mechanically with respiration. The pleural fluid is an exudate with a low glucose concentration (10-50 mg/dL) because of impaired transport of glucose into the pleural space. Pulmonary nodules may appear singly or in clusters. They typically develop in persons with peripheral rheumatoid nodules. Single nodules have the appearance of a coin lesion. The nodules typically are pleural based and may cavitate and create a bronchopleural fistula.

Pulmonary interstitial fibrosis is a chronic, slowly progressive disease process that usually occurs later in the course of seropositive RA. Interstitial disease is highly associated with smoking. This disease has physical findings of diffuse dry crackles on lung auscultation and a reticular nodular radiographic pattern affecting both lung fields, initially in the lung bases. Pulmonary function tests show a decrease in the diffusing capacity for carbon dioxide and a restrictive pattern. Bronchiolitis obliterans with or without cryptogenic organizing pneumonia may occur with RA or its treatment. Bronchiolitis obliterans produces an obstructive picture on pulmonary function testing and typically responds to corticosteroid treatment. High-resolution computed tomography is useful for distinguishing these different interstitial rheumatoid lung syndromes and predicting the treatment response. Lung biopsy is rarely necessary. Methotrexate treatment may cause a hypersensitivity lung reaction for 1% to 3% of patients. It usually presents in a subacute pattern, which may help to distinguish it from rheumatoid lung disease.

Key Definition

Pulmonary interstitial fibrosis: *a chronic, slowly progressive process usually occurring later in the course of seropositive rheumatoid arthritis.*

Cardiac Complications

Patients rarely present with acute pericarditis or tamponade. Recurrent effusive pericarditis without symptoms may evolve to chronic constrictive pericarditis. Signs of unexplained edema, ascites, or right heart failure may be the presenting manifestations of chronic seropositive RA. Chronic constrictive pericarditis will not respond to medical therapies; surgical pericardiectomy is necessary. The most common cardiac complication of patients with RA is increased risk of coronary artery disease.

Liver Abnormalities

Patients with RA can have increased levels of liver enzymes, particularly alkaline phosphatase. Increased levels of aspartate aminotransferase, γ-glutamyltransferase, and acute-phase proteins and hypoalbuminemia also occur in active RA. Liver biopsy shows nonspecific changes caused by inflammation. Nodular regenerative hyperplasia is rare and causes portal hypertension and hypersplenism. Many medications used to treat RA may cause increased levels of the transaminases.

Ophthalmic Abnormalities

Keratoconjunctivitis sicca, or secondary Sjögren syndrome, is the most common ophthalmic complication in RA. Scleritis, although rare, represents an ophthalmologic emergency for patients who have seropositive RA. It must be distinguished from benign episcleritis. Topical and systemic therapy is necessary in scleritis to avoid potential scleral perforations. Retinopathy is an infrequent complication of long-term hydroxychloroquine therapy.

Box 83.2 • Diseases That May Have Positive Rheumatoid Factor

- Rheumatoid arthritis[a]
- Sjögren syndrome[a]
- Hepatitis C
- Mixed cryoglobulinemia[a]
- Idiopathic pulmonary fibrosis
- Subacute bacterial endocarditis[a]
- Systemic lupus erythematosus
- Viral infections

[a] Diseases most likely to have high titer for rheumatoid factor.

Laboratory Findings

Nonspecific alterations are common in many laboratory values. In active RA disease, common laboratory results are normocytic anemia (hemoglobin value of about 10 g/dL), leukocytosis, thrombocytosis, hypoalbuminemia, and hypergammaglobulinemia. Rheumatoid factor is an immunoglobulin (Ig) directed against the Fc portion of IgG. It is detected in 70% to 80% of patients with RA. Rheumatoid factor is not specific for RA; its prevalence increases with aging among healthy persons. It also may be detected in other inflammatory diseases, such as primary Sjögren syndrome, systemic lupus erythematosus, mixed cryoglobulinemia, hepatitis C, and systemic vasculitis.

Some of the most likely diseases to have high titers of rheumatoid factor are RA and Sjögren syndrome (Box 83.2). Among the general US population, 5% have a low titer of rheumatoid factor. Anti-CCP antibodies are more specific for RA than rheumatoid factor and may be present when rheumatoid factor is absent. Antinuclear antibodies (ANAs) are common in seropositive rheumatoid disease. C-reactive protein correlates with disease activity, but it is not more helpful than the erythrocyte sedimentation rate. Active RA is associated with anemia of chronic disease, characterized by low iron-binding capacity, low plasma levels of iron, and an increased ferritin value. A normal ferritin value in this clinical setting suggests a component of iron deficiency anemia.

On aspiration, synovial fluid in RA is cloudy and light yellow, has poor viscosity, and typically contains 10,000 to 75,000 leukocytes/mL, predominantly neutrophils.

Radiographic Findings

The radiographic findings in early RA are either normal or show soft tissue swelling and periarticular osteopenia. Later, the characteristic changes of periarticular osteoporosis, symmetrical narrowing of the joint space, and marginal bony erosions become obvious. These findings are most commonly seen in radiographs of the hands, wrists, and forefeet. Baseline radiographs of these areas are part of the initial evaluation of newly diagnosed RA, both to assess severity of disease at presentation and to monitor progression of disease over time.

Diagnosis

Adult RA should be considered when a person older than 16 years has inflammatory joint symptoms that last for more than 6 weeks (Figure 83.2). The time criterion is important because certain viral arthropathies, such as parvovirus B19 infection, mimic acute RA. Hallmark features of early RA include morning stiffness lasting for more than 30 minutes, symmetrical involvement in the metatarsophalangeal joints, and tenderness and swelling of metacarpophalangeal joints.

The common conditions in the differential diagnosis of seronegative RA are listed in Table 83.1.

Acute-onset oligoarticular seronegative RA needs to be distinguished from reactive arthritis, sarcoid, and Lyme arthritis. Sausage digits, or dactylitis, are often associated with the spondyloarthropathy disorders, usually involve the spine and lower extremities, and are asymmetrical. A synovial fluid analysis should always be done to exclude crystalline arthritis, gout, and calcium pyrophosphate. The detection of CCP antibody has allowed rheumatologists to identify RA early in the clinical evolution of the disease, before patient characteristics would meet the classification criteria for established RA.

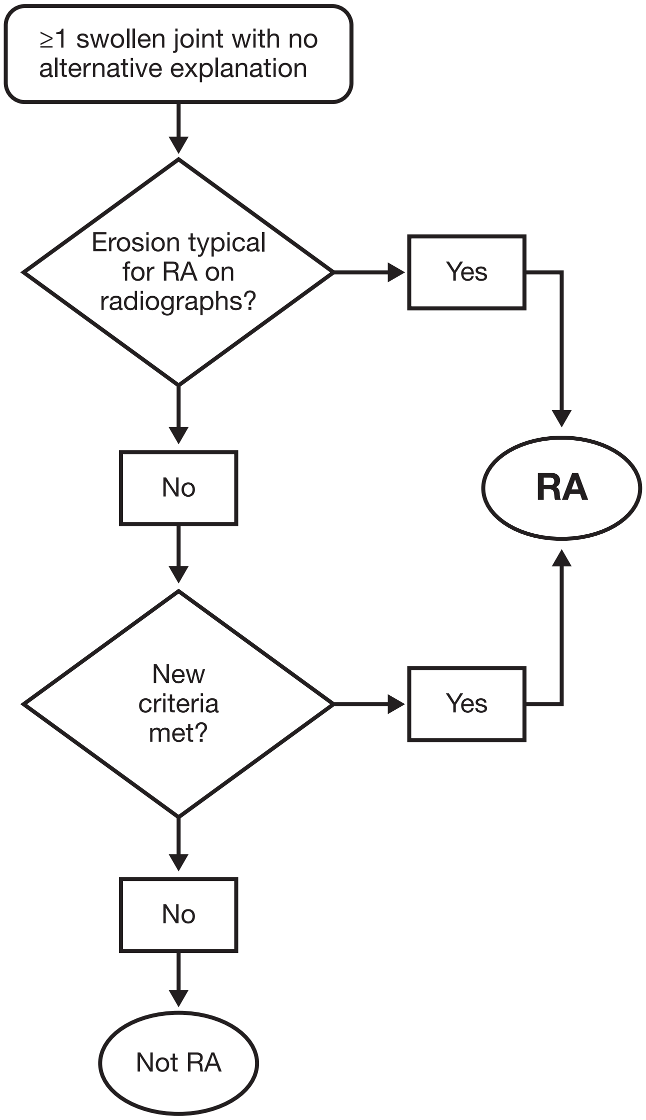
Treatment

The management of RA requires identifying RA early, and starting appropriate therapy as soon as possible to prevent joint damage and maintain function. A treat-to-target strategy is now recommended for patients with RA. Treatment should be closely managed and advanced with the goal of remission or, at a minimum, low disease activity based on a targeted disease activity score.

Disease-modifying agents are usually first-line therapy. For patients with seropositivity, methotrexate is the drug of choice. The dose is gradually increased over 6 to 8 weeks to a target dose of 15 to 25 mg once weekly. Folic acid is given daily as a supplement to reduce drug toxicities. For patients who do not tolerate methotrexate, leflunomide or sulfasalazine is an alternative. The presence of chronic kidney or liver disease influences the choice and dose of all 3 agents. Methotrexate and leflunomide are contraindicated in women of childbearing age who are not using reliable contraception.

For patients with seronegative RA who do not have erosive disease, hydroxychloroquine is an option as first therapy. Tapered oral corticosteroid therapy is recommended in some protocols for early RA while disease-modifying antirheumatic drug therapies are initiated. In the patient for whom methotrexate monotherapy does not produce a response within 3 months, add-on intervention is recommended. Options include triple therapy with the addition of hydroxychloroquine and sulfasalazine or, alternatively, a biologic agent.

In the past 2 decades, biologic agents have revolutionized the treatment of RA. The first class discovered among the biologic


≥1 swollen joint with no alternative explanation
Erosion typical for RA on radiographs?
Yes
No
RA
New criteria met?
Yes
No
Not RA

Joint Involvement (0-5)	Points
1 large joint	0
2-10 large joints	1
1-3 small joints (large joints not counted)	2
4-10 small joints (large joints not counted)	3
>10 joints (>1 small joint)	5
Serology (0-3)	
RF negative and ACPA negative	0
RF weakly positive (1-3 x N) or ACPA weakly positive (1-3 x N)	2
RF strongly positive (>3 x N) or ACPA strongly positive (>3 x N)	3
Symptom Duration (0-1)	
<6 weeks	0
≥6 weeks	1
Laboratory Tests for Inflammation (0-1)	
CRP = N **and** ESR = N	0
CRP abnormal **or** ESR abnormal	1

RA if Score ≥6

Figure 83.2. Classification Criteria for Rheumatoid Arthritis (RA), Suggested by the American College of Rheumatology and European League Against Rheumatism 2010. ACPA indicates anti–citrullinated protein antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; N, normal; RF, rheumatoid factor.

(Modified from Gaujoux-Viala C, Gossec L, Cantagrel A, Dougados M, Fautrel B, Mariette X, et al; French Society for Rheumatology. Recommendations of the French Society for Rheumatology for managing rheumatoid arthritis. Joint Bone Spine. 2014 Jul;81[4]:287-97. Epub 2014 Jun 27 as modified from original: Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010 Sep;69[9]:1580-8. Erratum in: Ann Rheum Dis. 2010 Oct;69[10]:1892; used with permission.)

agents effective against RA is the TNF inhibitors, and therefore, these are often the first biologic agent prescribed. Currently, 5 TNF agents have been approved for RA by the US Food and Drug Administration: etanercept, infliximab, adalimumab, golimumab, and certolizumab. The main adverse effects from TNF inhibitors are increased infection risk, exacerbation of stage 3 to stage 4 congestive heart failure, and demyelinating disease. Importantly, tuberculosis screening should be obtained before initiation of a TNF agent; immunizations also should be updated before the initiation of biologics. Other biologic therapies include targets against IL-1 and IL-6, T-cell targets, B-cell targets, and small-molecule Janus kinase targets. The decision regarding the use of biologic therapies should be left to the consulting rheumatologist.

Preventive medical care is essential in RA management Assessment for coronary artery disease risk factors and

Table 83.1 • Differential Diagnosis of Seronegative Polyarthritis

- Infectious arthritis
  - Bacterial (eg, Lyme, SBE, Whipple)
  - Viral (eg, Chikungunya fever, hepatitis B and hepatitis C, parvovirus)
- Reactive (postinfectious)
  - Enteric infection
  - Reactive arthritis
  - Rheumatic fever
- Other seronegative spondyloarthropathies
  - Ankylosing spondylitis
  - Inflammatory bowel disease
  - Psoriatic arthritis
- Inflammatory osteoarthritis
- Crystal-induced arthritis
- Systemic rheumatic illnesses
  - Autoinflammatory disorders
  - Behçet syndrome
  - PM/DM
  - Polymyalgia rheumatica
  - Relapsing polychondritis
  - Scleroderma
  - Systemic lupus erythematosus
  - Still disease
  - Vasculitis
- Other systemic illnesses
  - Amyloid arthropathy
  - FMF
  - Hemochromatosis
  - Hypothyroidism
  - Malignancy
  - Multicentric reticulohistiocytosis
  - Sarcoidosis

Abbreviations: FMF, familial Mediterranean fever; PM/DM, polymyositis or dermatomyositis; SBE, subacute bacterial endocarditis.

appropriate interventions are strongly recommended. Patients who have RA are at increased risk for osteoporosis. Vaccinations should be current, but patients receiving biologic therapies should not receive live vaccines.

An orthopedic surgical procedure for RA continues to be an important therapeutic option for preservation or enhancement of function. Synovectomy of the extensor wrist and nearby tendon sheaths is beneficial when medication alone fails to control the synovitis. Synovectomy of other joints has become less necessary as medical therapies have advanced. Resection of uncomfortable, draining, or infected nodules and decompression of refractory carpal tunnel syndrome are also important surgical treatments of RA. Arthroplasty is reserved for patients for whom medical management has failed and who have intractable pain or compromise in function because of a destroyed joint. Joint replacement has had a major effect on the reduction of patient disability. Preoperative cardiac assessment is necessary for a patient with RA because of the well-established cardiovascular risk of this patient.

Conditions Related to RA

Seronegative RA

Rheumatoid factor–negative (seronegative) RA is usually not associated with extra-articular manifestations. However, the arthritis usually is destructive, deforming, and otherwise indistinguishable from seropositive RA. Erosive seronegative RA is managed similarly to seropositive disease.

Some patients older than 60 years with seronegative RA may have milder arthritis. In this subgroup, polyarticular inflammation suddenly develops and is controlled best with low doses of prednisone. The presence of anti-CCP antibodies and foot and ankle synovitis may help distinguish late-onset RA from polymyalgia rheumatica. Minimal destructive changes and deformity occur. Some elderly patients with seronegative arthritis, such as men in their 70s, present with acute polyarthritis and pitting edema of the hands and feet, so-called remitting symmetrical seronegative synovitis with pitting edema (RS3PE). They have a prompt and gratifying response to low doses of prednisone. RS3PE typically runs a course similar to that of polymyalgia rheumatica. A refractory seronegative inflammatory arthritis in an elderly person may also represent a paraneoplastic syndrome.

Adult-Onset Still Disease

Systemic juvenile RA is known as *Still disease*. It has quotidian (fever spike with return to normal all in 1 day) high-spiking fevers, arthralgia, arthritis, seronegativity (negativity for rheumatoid factor and ANA), leukocytosis, macular evanescent rash, serositis, lymphadenopathy, splenomegaly, and hepatomegaly. Fever, rash, and arthritis are the classic triad of Still disease.

Adult-onset Still disease has a slight female predominance. Its onset typically occurs between ages 16 and 35 years. Temperature more than 39°C occurs in a quotidian or double quotidian pattern in 96% of patients. The rash has a typical appearance: a macular salmon-colored eruption on the trunk and extremities. This transient rash is usually noticed at the time of the increased temperature. Arthritis occurs in 95% of affected patients. In one-third of these patients, the joint disease is progressive and destructive. Adult-onset Still disease has a predilection for the wrists, shoulders, hips, and knees. Among patients, 60% report a sore throat at onset, which can confuse the diagnosis with rheumatic fever; however, the course is much more prolonged than that of acute rheumatic fever. Weight loss is common.

Lymphadenopathy occurs in two-thirds of patients, and hepatosplenomegaly in about one-half. Pleurisy, pneumonitis, and abdominal pain occur in less than one-third of patients. The serum ferritin level is markedly increased.

Treatment of adult-onset Still disease includes NSAIDs. Corticosteroids may be needed to control the systemic symptoms. One-half of patients require methotrexate to control the systemic and articular features. IL-1 inhibitor therapy is useful for the management of resistant cases.

Felty Syndrome

Felty syndrome has the classic triad of RA, leukopenia related to neutropenia, and splenomegaly (Box 83.3). Classic Felty syndrome usually occurs after 12 years or more of RA. It develops in less than 1% of patients with seropositive RA. Splenomegaly either may not be clinically apparent or may manifest only after the arthritis and leukopenia have been present for some time. Patients with this syndrome frequently have bacterial infections, particularly of the skin and lungs. Infection related to the cytopenia is the major cause of death. High titers of rheumatoid factor are the rule, and two-thirds of patients are positive for ANA. Patients often die of sepsis despite vigorous antibacterial treatment. Treatment can include corticosteroids, methotrexate, granulocyte colony-stimulating factor, and splenectomy. Differential diagnosis includes the large granular lymphocyte syndrome. Affected patients frequently have neutropenia with a normal total white cell count related to the lymphocytosis.

KEY FACTS

- ✓ Patients with RA have increased risk of coronary artery disease
- ✓ Serologic testing for acute parvovirus should be done for patients who present with an acute small-joint polyarthritis
- ✓ A diagnosis of seropositive RA mandates immediate therapy with a disease-modifying antirheumatic drug, most commonly methotrexate
- ✓ Early therapy for seropositive RA has improved survival and reduced the prevalence of many extra-articular complications

Box 83.3 • Features of Felty Syndrome

Classic triad
    Seropositive rheumatoid arthritis
    Neutropenia with leukopenia
    Splenomegaly
Other
    Recurrent fevers with and without infection
    Lower-extremity ulcers

Spondyloarthritis

Conditions in the spondyloarthritis spectrum include axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis), reactive arthritis (Reiter syndrome), arthritis related to inflammatory bowel disease, and psoriatic arthritis. However, most patients are not neatly categorized into any of these classic disorders and instead are categorized as having undifferentiated spondyloarthritis. These patients may have varied manifestations of spondyloarthritis but do not have one of the classic diseases. Patients may have predominantly axial or peripheral involvement. An example is refractory Achilles enthesitis and plantar fasciitis, *HLA-B27* positive.

Spondyloarthritis is characterized by the following 7 clinical situations: involvement of the sacroiliac joints (uncommon in RA); peripheral arthritis that is usually asymmetrical and oligoarticular; absence of rheumatoid factor; acute anterior uveitis; association with *HLA-B27*; an enthesopathy (disorder of muscle or tendinous attachment to bones); and dactylitis. Family history of similar disorders, psoriasis, or inflammatory bowel disease may be reported.

Spondyloarthritis is associated with the *HLA-B27* gene on chromosome 6. The prevalence of *HLA-B27* determines the frequency of ankylosing spondylitis in various populations. In randomly selected persons with *HLA-B27*, the chance of spondyloarthritis is 2%. In *HLA-B27*–positive relatives of *HLA-B27*–positive patients with ankylosing spondylitis, the risk of spondyloarthritis is 20% (Box 83.4).

Axial Spondyloarthritis

Axial spondyloarthritis is a chronic systemic inflammatory disease that affects the sacroiliac joints, the spine, and the peripheral joints. Patients with axial spondyloarthritis may have either radiographic evidence of sacroiliitis (ankylosing spondylitis) or MRI evidence of sacroiliitis without radiographic findings (nonradiographic axial spondyloarthritis). Sacroiliitis and inflammatory low back pain define this disease.

Key Definition

Axial spondyloarthritis: *a chronic systemic inflammatory disease that affects the sacroiliac joints, the spine, and the peripheral joints.*

Box 83.4 • Rheumatic Diseases Associated With *HLA-B27*

Axial spondyloarthritis (90%)
Reactive arthritis (>80%)
Enteropathic spondylitis (approximately 75%)
Psoriatic spondylitis (approximately 50%)

Abbreviation: HLA, human leukocyte antigen.

Features

Characteristic features of inflammatory low back pain in axial spondyloarthritis have an age at onset usually between 15 and 40 years, insidious onset, duration of more than 3 months, morning stiffness that improves with exercise but not with rest, and night pain improved by getting out of bed. Response to anti-inflammatory medication is also suggestive of an early spondyloarthritis.

Findings of axial spondyloarthritis on physical examination can include chest expansion of less than 5 cm (Table 83.2). Other physical findings of this spondyloarthritis are listed in Table 83.3. Patients with ankylosing spondylitis tend to have more extensive spinal involvement than those with nonradiographic disease. Radiographic findings in ankylosing spondylitis include sacroiliac sclerosis and possible erosions, spine involvement with squaring of the vertebral bodies, syndesmophytes, and so-called bamboo spine. These findings may take years to appear. For patients with nonradiographic disease, MRI can detect inflammation in the sacroiliac joints, which may progress over years to become evident on radiographs.

Laboratory Findings

The erythrocyte sedimentation rate or C-reactive protein value may be increased in axial spondyloarthritis. The patient may have an anemia of chronic disease, and 95% of white patients are positive for *HLA-B27*. Rheumatoid factor is absent.

Extraspinal Involvement

Enthesopathic involvement is characteristic of the spondyloarthropathies and includes plantar fasciitis, Achilles tendinitis, and trochanteric enthesitis. Hip, shoulder, and chest wall involvement is common, but peripheral joints can also be affected, usually with asymmetrical involvement of the lower extremities.

Extraskeletal Involvement

Other findings in active spondyloarthritis disease include fatigue, weight loss, uveitis, and low-grade fever. Uveitis is an important clue to the diagnosis of spondyloarthritis and is not found in adults with RA. Osteoporosis is a common complication of ankylosing spondylitis and can occur in early stages of the disease. Late complications can be traumatic spinal fracture leading to cord compression, cauda equina syndrome (symptoms include neurogenic bladder, fecal incontinence, and radicular leg pain), fibrotic changes in upper lung fields, aortic insufficiency, complete heart block, and secondary amyloidosis.

Table 83.2 • Results of Testing in Axial Spondyloarthritis

Test	Method	Results
Schober	Make a mark on the spine at level of L5 and one at 10 cm directly above, with the patient standing erect. Patient then bends forward maximally, and the distance between the 2 marks is measured	An increase <5 cm indicates early lumbar involvement. Not helpful in older adults with degenerative spondylosis
Chest expansion	Measure maximal chest expansion at nipple line	Chest expansion <5 cm is a clue to early costovertebral involvement

Table 83.3 • Findings in Axial Spondyloarthritis

Characteristic	Finding
Scoliosis	Absent
Decreased range of movement	Symmetrical
Tenderness	Diffuse
Hip flexion with straight-leg raising	Normal
Pain with sciatic nerve stretch	Absent
Hip involvement	Frequently present
Neurodeficit	Absent

Differential Diagnosis

The differential diagnosis of spondyloarthritis includes diffuse idiopathic skeletal hyperostosis, osteitis condensans ilii, and degenerative spondylosis. The clinical symptoms of diffuse idiopathic skeletal hyperostosis are reported "stiffness" of the spine and relatively good preservation of spine motion. Spondyloarthritis generally affects middle-age and elderly men. Patients with diffuse idiopathic skeletal hyperostosis can have dysphagia related to cervical osteophytes. Criteria for the condition are flowing ossification along the anterolateral aspect of at least 4 contiguous vertebral bodies, preservation of disk height, absence of apophyseal joint involvement, absence of sacroiliac joint involvement, and extraspinal ossifications, including ligamentous calcifications.

Osteitis condensans ilii affects young to middle-aged women who have normal sacroiliac joints. Radiography shows asymptomatic sclerosis on the iliac side of the sacroiliac joint only. The sacroiliac joint also can be involved with tuberculosis, metastatic disease, Paget disease, or other infections (eg, *Brucella, Serratia, Staphylococcus*).

Treatment

Treatment of axial spondyloarthritis involves physical therapy (upright posture is very important), exercise (low impact), cessation of smoking, genetic counseling, and drug therapy with NSAIDs. TNF inhibitors can provide benefit for refractory spinal and peripheral joint symptoms. They are also effective for managing refractory uveitis.

Reactive Arthritis

Reactive arthritis is an aseptic arthritis induced by a host response to an infectious agent rather than a direct infection. *HLA-B27* is associated with 80% of cases. Reactive arthritis develops after infections with *Salmonella, Shigella flexneri, Yersinia enterocolitica, Campylobacter jejuni, Clostridium difficile*, and *Chlamydia trachomatis*. Chlamydia infections may be asymptomatic. Inflammatory eye disease (conjunctivitis or uveitis) and mucocutaneous disease (balanitis, oral ulcerations, or keratoderma) can occur. Keratoderma blennorrhagicum is a characteristic skin disease on the palms and soles that is indistinguishable histologically from psoriasis. Joint predilection is for the toes and the asymmetrical large joints in the lower extremities. Presentation may be acute, requiring consideration of gout and septic arthritis in the differential diagnosis. Dactylitis and enthesitis are found and are similar to what occurs in psoriatic arthritis. Reactive arthritis is frequently self-limited, but it conveys a risk of chronic arthritis.

Treatment is with NSAIDs. Sulfasalazine, methotrexate, and TNF inhibitors are given for patients with persistent disease. Prolonged antibiotic therapy of *Chlamydia*-triggered reactive arthritis continues to be controversial.

Arthritis Associated With Inflammatory Bowel Disease

Oligoarthritis of the peripheral joints and enteropathic spondylitis are the 2 distinct types of arthritis associated with chronic inflammatory bowel disease (Box 83.5).

For patients with these types of arthritis, NSAIDs must be used with caution because they may result in a flare of the bowel disease. Infliximab, certolizumab, and adalimumab are the drugs of choice to treat both spondylitis and Crohn disease. Etanercept is not beneficial for Crohn disease. The peripheral arthritis often remits as the active bowel inflammation is treated.

Box 83.5 • The Distinct Types of Arthritis Associated With Chronic Inflammatory Bowel Disease

Oligoarthritis of the peripheral joints
- Tends to correlate with bowel disease activity
- At presentation, the bowel disease, especially Crohn disease, may be asymptomatic
- Other clues (eg, recurrent erythema nodosa, iron deficiency) may suggest occult inflammatory bowel disease

Enteropathic spondylitis
- Does not reflect activity of the bowel disease, and its subsequent progress bears little relation to the bowel disease
- Approximately 75% of patients with enteropathic spondylitis and inflammatory bowel disease have positivity for HLA-B27

Abbreviation: HLA, human leukocyte antigen.

Psoriatic Arthritis

Psoriatic arthritis develops in approximately 15% of patients with psoriasis. Dactylitis of the finger or toe is characteristic of psoriatic arthritis. A patient presenting with dactylitis should be carefully examined for psoriasis, including the scalp, gluteal cleft, groin, and umbilicus. Patients with HIV infection may present with severe, refractory psoriasis and psoriatic arthritis.

Most patients present with monoarticular or oligoarticular disease but eventually have polyarticular engagement. Involvement of the distal interphalangeal joint with adjacent nail psoriasis is a classic finding, but it is not always present. The extent of the psoriasis and the joint involvement frequently do not correspond. Axial spinal involvement may be more limited than in ankylosing spondylitis. Unlike in RA, radiographs often show both new bone formation (periostitis) and erosions. Pencil-in-cup deformity of the distal and proximal interphalangeal joints is found on radiographs in advanced disease.

Treatment is with NSAIDs, methotrexate, and TNF inhibitors. Newer medications approved by the US Food and Drug Administration for treatment of psoriatic arthritis include monoclonal antibodies (targeting IL-17 and IL-23) and a phosphodiesterase inhibitor.

Uveitis and Rheumatologic Diseases

Various rheumatologic diseases are associated with uveitis, particularly the spondyloarthritis disorders. Uveitis is uncommon in RA and systemic lupus erythematosus. Nongranulomatous uveitis with no other associated symptoms may be associated with *HLA-B27* in almost 50% of patients. Other causes of uveitis include sarcoidosis, Behçet syndrome, polychondritis, and juvenile idiopathic arthritis, especially in young women who have ANA positivity.

Behçet Syndrome

The common manifestations of Behçet syndrome are oral and genital ulcers and uveitis. Behçet syndrome is most common in Middle Eastern countries and Japan. HLA-B51 is associated with the syndrome. Uveitis, synovitis, cutaneous vasculitis, and meningoencephalitis may be present. Treatment is with corticosteroids, although more aggressive immunosuppression often is required. In North American white persons, the primary differential diagnosis is Crohn disease.

KEY FACTS

- ✓ Characteristics of spondyloarthritis—asymmetrical, predominantly lower-extremity synovitis, involvement of the sacroiliac joints (uncommon in RA), peripheral arthritis that is usually oligoarticular, inflammatory spine pain, absence of rheumatoid factor, acute anterior uveitis, association with HLA-B27, enthesopathy, and dactylitis
- ✓ Enthesitis, dactylitis, iritis, psoriasis, and inflammatory bowel disease distinguish spondyloarthritis from RA
- ✓ Characteristics of inflammatory low back pain in ankylosing spondylitis—age at onset usually between 15 and 40 years, insidious onset, duration of more than 3 months, morning stiffness that improves with exercise but not with rest, and night pain improved by getting out of bed
- ✓ Reactive arthritis—develops after infection with *Salmonella, Shigella flexneri, Yersinia enterocolitica, Campylobacter jejuni, Clostridium difficile*, and *Chlamydia trachomatis*
- ✓ Involvement of the distal interphalangeal joint with adjacent nail psoriasis—classic finding of psoriatic arthritis but not always present

84 Vasculitis

MATTHEW J. KOSTER, MD; KENNETH J. WARRINGTON, MD

Vasculitis

Vasculitis refers to a group of autoimmune disorders characterized by inflammation of blood vessels. The inflammatory process results in vascular damage with stenosis or occlusion of the vessel lumen and consequent end-organ ischemia. Vasculitis also may weaken the arterial wall, resulting in progressive vascular dilatation and aneurysm formation. The distribution of vascular lesions differs considerably among the different vasculitic syndromes. Vasculitis can be classified according to the predominant type of vessel involved (referred to as large vessel, medium vessel, or small vessel vasculitis) (Box 84.1). Most forms of vasculitis are chronic systemic disorders that cause multiorgan damage; yet, vasculitis may be localized to a single organ. The cause of vasculitis is generally unknown, but viral infections, certain medications, and malignancies trigger some forms of vasculitis.

Key Definition

Vasculitis: *autoimmune disorder characterized by inflammation of blood vessels.*

Vasculitis also may occur as a complication of an underlying rheumatologic disorder, such as rheumatoid arthritis or systemic lupus erythematosus. The clinical manifestations of vasculitis are variable and depend on the pattern of vascular involvement. Indeed, vasculitis should be considered in the differential diagnosis of any multisystem illness. Vasculitis mimics should also be considered whenever vasculitis is suspected (Box 84.2). The initial evaluation and common test abnormalities for patients with vasculitis are listed in Box 84.3. The ability to recognize characteristic clinical patterns of the disease is helpful for making the diagnosis of systemic vasculitis.

Large Vessel Vasculitis

Giant Cell Arteritis

Giant cell arteritis (GCA), previously known as *temporal arteritis*, predominantly affects persons of North European ancestry who are older than 50 years. Women are affected by GCA 2 to 3 times as often as men. GCA is one of the most common forms of vasculitis in adults, with an annual incidence of about 19 cases per 100,000 people age 50 years or older. The lifetime risk of GCA has been estimated to be about 1% for women and 0.5% for men.

Pathologic Characteristics

The vasculitic process typically involves the extracranial branches of the carotid artery and frequently also affects the aorta and the aortic arch branches. The exact cause of GCA is unknown; however, genetic and environmental factors are likely involved in its pathogenesis. The histologic findings in GCA consist of mononuclear cell infiltrates that involve all 3 layers of the arterial wall (intima, media, and adventitia). Multinucleated giant cells are seen in 50% of cases, generally in association with a fragmented internal elastic lamina. The inner layer of the artery undergoes concentric fibrointimal proliferation, which results in luminal stenosis.

Clinical Features

Although the clinical features of GCA (Box 84.4) can differ, patients typically present with new-onset headache and scalp

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Portions of the Clinical Features section on polyarteritis nodosa were previously published in Friese JL, Warrington KJ, Miller DV, Ytterberg SR, Fleming CJ, Stanson AW. Polyarteritis nodosa (PAN). In: Hendaoui L, Stanson AW, Bouhaouala MH, Joffre F, editors. Systemic vasculitis: imaging features. Berlin (Germany): Springer-Verlag; c2012. p. 189-207. (Medical radiology: diagnostic imaging series); used with permission.

Box 84.1 • Nomenclature Vasculitides[a]

- Large vessel vasculitis
  - Takayasu arteritis
  - Giant cell arteritis
- Medium vessel vasculitis
  - Polyarteritis nodosa
  - Kawasaki disease
- Small vessel vasculitis (SVV)
  - Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis
    - Microscopic polyangiitis
    - Granulomatosis with polyangiitis (formerly Wegener granulomatosis)
    - Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)
  - Immune complex SVV
    - Anti–glomerular basement membrane disease
    - Cryoglobulinemic vasculitis
    - IgA vasculitis (Henoch-Schönlein purpura)
    - Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)
- Variable vessel vasculitis
  - Behçet disease
  - Cogan syndrome
- Single-organ vasculitis
  - Cutaneous leukocytoclastic angiitis
  - Cutaneous arteritis
  - Primary central nervous system vasculitis
  - Isolated aortitis
  - Others
- Vasculitis associated with systemic disease
  - Lupus vasculitis
  - Rheumatoid vasculitis
  - Sarcoid vasculitis
  - Others
- Vasculitis associated with probable cause
  - Hepatitis C virus–associated cryoglobulinemic vasculitis
  - Hepatitis B virus–associated vasculitis
  - Syphilis-associated aortitis
  - Drug-associated immune complex vasculitis
  - Drug-associated ANCA-associated vasculitis
  - Cancer-associated vasculitis
  - Others

Abbreviation: IgA, immunoglobulin A.

[a] Adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides.

From Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013 Jan;65(1):1-11; used with permission.

Box 84.2 • Conditions That Mimic Vasculitis

- Cardiac myxoma with embolization
- Fibromuscular dysplasia
- Infective endocarditis
- Thrombotic thrombocytopenic purpura
- Atheroembolism, cholesterol emboli
- Ergotism
- Hereditary disorders of the connective tissues (eg, pseudoxanthoma elasticum, vascular type of Ehlers-Danlos syndrome, Marfan syndrome)
- Antiphospholipid syndrome
- Livedoid vasculopathy
- Arterial coarctation
- Bacteremia
- Malignancy (eg, intravascular lymphoma)
- Rickettsial infection
- Chronic infections (eg, hepatitis, HIV infection, tuberculosis)

Box 84.3 • Initial Evaluation of Patients With Suspected Vasculitis

- Complete blood cell count (anemia is common)
- ESR (frequently increased)
- CRP (frequently increased)
- Creatinine (increased with renal involvement)
- Urinalysis with microscopic examination (hematuria, RBC casts, dysmorphic RBCs with renal involvement)
- Liver enzymes (may be increased)
- ANCA screen (positive in some forms of small vessel vasculitis)
- RF, CCP antibody, ANA (may be positive if underlying rheumatic disease)
- Complement (total complement, C3, and C4 may be decreased in some forms of vasculitis)
- Cryoglobulins (positive in cryoglobulinemic vasculitis)
- Hepatitis B and C serologies (if positive, consider hepatitis-associated vasculitis)
- Chest radiograph (evaluate for infiltrates, nodules, and effusion)
- Vascular imaging (CTA or MRA) if medium vessel or large vessel vasculitis is suspected
- Nerve conduction studies (if neuropathy is suspected)
- Additional imaging or organ-specific evaluation depending on clinical presentation

Abbreviations: ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; CTA, computed tomographic angiography; ESR, erythrocyte sedimentation rate; MRA, magnetic resonance angiography; RBC, red blood cell; RF, rheumatoid factor.

Box 84.4 • Clinical Features of Giant Cell Arteritis

- Symptoms
  - Constitutional
    - Fever, fatigue, weight loss, anorexia
  - Polymyalgia rheumatica
    - Aching and stiffness of the neck, shoulders, hips, and proximal extremities
  - Cranial
    - Temporal headache
    - Scalp tenderness
    - Jaw or tongue claudication
    - Impaired vision, diplopia, amaurosis fugax, vision loss
  - Large vessel disease
    - Arm claudication
- Signs
  - Musculoskeletal
    - Pain with range of motion of neck, shoulders, and hips
  - Cranial
    - Temporal artery tenderness
    - Absent temporal artery pulse
  - Large vessel disease
    - Decreased or absent radial artery pulse
    - Asymmetrical arm blood pressures
    - Bruits (carotid and subclavian arteries)
    - Aortic regurgitation murmur (may indicate dilated ascending aorta)

tenderness in the context of a systemic inflammatory syndrome. Polymyalgia rheumatica (PMR) symptoms (aching and stiffness of the neck, shoulders, hips, and proximal extremities) occur in about 40% of patients with GCA. Although present in only about one-third of patients, jaw claudication is highly specific for GCA. Ocular symptoms may develop (ie, decreased vision, diplopia, and amaurosis fugax), and in up to 15% of patients, permanent vision loss results from ischemic optic neuropathy. Neurologic manifestations are uncommon and may include stroke, transient ischemic attack, or neuropathy. Patients with large vessel GCA (involving the aorta and arch branches) often present with constitutional symptoms, claudication of the upper extremities, or asymmetrical blood pressures. Physical examination should include a careful assessment of the temporal arteries and peripheral vessels for pulses and bruits.

Diagnosis

Markers of inflammation, including the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, are often considerably increased in GCA. Although some patients may have a normal ESR, the CRP level is almost always elevated. Patients may have other, nonspecific laboratory abnormalities, such as normocytic anemia, increased platelet count, and abnormal liver function test results. The gold standard diagnostic test for GCA is histopathologic examination of a temporal artery biopsy specimen. In a subset of patients with GCA (particularly those with large vessel disease), temporal artery biopsy findings may be negative. For these patients, GCA affecting the aorta and its branches may be diagnosed with magnetic resonance angiography (MRA) or computed tomographic angiography (CTA). In select cases, positron emission tomography (PET) can be used to detect vascular inflammation in large arteries (Figure 84.1). The American College of Rheumatology has developed classification criteria for GCA (Box 84.5).

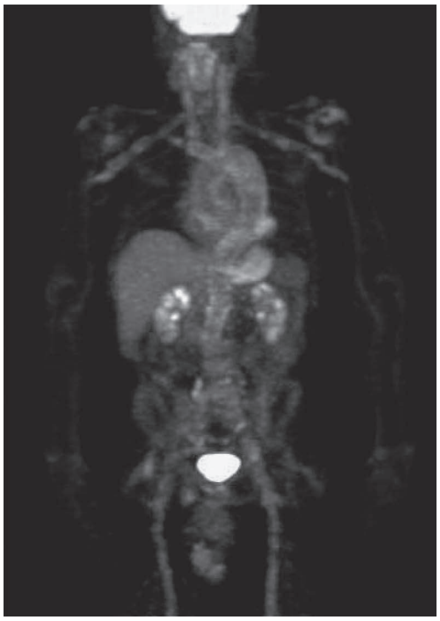

Figure 84.1. *Large Vessel Vasculitis. Positron emission tomographic scan shows fludeoxyglucose F 18 uptake in the aorta and major branches, consistent with large vessel vasculitis.*

Treatment

Treatment with corticosteroids should be initiated promptly when the diagnosis of GCA is suspected. Temporal artery biopsy should not delay treatment because histopathologic evidence of arteritis persists for several weeks after corticosteroid therapy has been started. The initial treatment dose of oral prednisone is typically 40 to 60 mg daily. A higher dose of intravenous corticosteroids can be given to patients with impending loss of vision. If patients have no contraindications to antiplatelet therapy, low-dose aspirin therapy should be started because it may reduce the risk of vision loss and cerebrovascular events. Measures to prevent or treat corticosteroid-related adverse effects are also an essential aspect of GCA management.

Box 84.5 • The American College of Rheumatology 1990 Criteria and Definitions for the Classification of GCA

For the classification of GCA, ≥3 of the following 5 criteria must be present (the presence of ≥3 criteria yields a sensitivity of 93.5% and a specificity of 91.2% for distinguishing GCA from other forms of vasculitis)

1. Age at disease onset ≥50 y—development of symptoms or findings beginning at age 50 y or older
2. New headache—new onset of or new type of localized pain in the head
3. Temporal artery abnormality—temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries
4. Increased ESR—ESR ≥50 mm/h by the Westergren method
5. Abnormal artery biopsy findings—biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

Abbreviations: ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis.

From Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990 Aug;33(8):1122-8; used with permission.

GCA is a chronic condition requiring treatment with corticosteroids, often for 1 to 2 years or longer. Disease relapses during corticosteroid tapering are common. Several corticosteroid-sparing agents have been evaluated with limited efficacy observed. Methotrexate therapy results in only a moderate decrease in relapse frequency and a modest reduction in corticosteroid exposure. Tocilizumab, a monoclonal antibody directed against interleukin 6 receptor, is the first immunosuppressive agent to show definitive benefit in the treatment of both newly diagnosed and relapsing GCA compared with corticosteroids alone. Tocilizumab (162 mg in subcutaneous injection weekly) is the first immunosuppressive agent to receive US Food and Drug Administration approval for treatment of GCA. Studies are ongoing to determine the required length of tocilizumab treatment and the long-term outcomes of patients receiving tocilizumab.

Outcome

Overall, the life expectancy of patients with GCA is similar to that of the general population. However, patients with GCA have an increased risk of aortic aneurysms, particularly of the thoracic aorta. Aneurysms generally develop 3 to 5 years after the GCA diagnosis and may lead to aortic dissection, with a high risk of death. Long-term monitoring for aortic aneurysms is therefore recommended.

Takayasu Arteritis

Takayasu arteritis (TAK) is a rare form of large vessel vasculitis that primarily affects the aorta and its major branches. TAK typically occurs in women younger than 40 years. The cause is unknown, but each year, 2 or 3 new cases occur per 1 million population. TAK has a worldwide distribution but is more common in persons of Asian ancestry. The histopathologic characteristics are similar to those of GCA. The upper extremity and neck arteries (carotid and vertebral) are most frequently affected. Renal, mesenteric, coronary, pulmonary, and lower extremity arterial involvement may also occur. Vascular inflammation results in arterial thickening with subsequent narrowing or occlusion of the lumen. Damage to the aorta may lead to dilatation and aneurysm formation.

Key Definition

Takayasu arteritis: *a rare form of large vessel vasculitis that primarily affects the aorta and its major branches.*

Clinical and Laboratory Features

Patients who have TAK often present with nonspecific constitutional symptoms, such as fatigue, malaise, arthralgia, and myalgias. Extremity claudication is a common concern. Compromise of the cerebral circulation can lead to amaurosis fugax, syncope, transient ischemic attack, or stroke. Patients with coronary artery involvement may present with anginal symptoms. Refractory hypertension may result from renal artery stenosis. Abdominal angina may indicate mesenteric ischemia due to visceral arterial involvement. Other manifestations may include erythema nodosum and inflammatory arthritis. Absence or asymmetry of upper-extremity pulses or lower-extremity pulses (or both) is often a characteristic of patients with TAK. Vascular bruits are common, and aortic valvular regurgitation may be present because of dilatation of the ascending aorta.

TAK has no specific biomarker; however, laboratory features of inflammation (ie, increased ESR and CRP level, anemia, and thrombocytosis) are generally detected. About one-third of patients may have normal inflammatory marker characteristics. The diagnosis is generally made with MRA or CTA. PET also can be useful to assess for vascular inflammation in the aorta and its main branches. Classification criteria for TAK are listed in Box 84.6.

Treatment and Outcome

Corticosteroids are the initial treatment of choice for TAK. Most patients require the addition of an immunosuppressive agent (ie, methotrexate, azathioprine, or mycophenolate mofetil) as the dose of corticosteroids is tapered. Refractory disease is generally treated with tumor necrosis factor inhibitors, and cyclophosphamide is used only in life-threatening disease. TAK is generally a chronic disease that requires ongoing

Box 84.6 • Classification Criteria for Takayasu Arteritis[a]

Age at disease onset ≤40 y

Claudication of upper extremities

Decreased brachial artery pulse

Blood pressure difference between arms ≥10 mm Hg

Aortic or subclavian bruit

Arteriographic abnormality of aorta, primary branches, or large arteries in the upper or lower extremities

[a] For purposes of classification, a patient shall be said to have Takayasu arteritis if at least 3 of the 6 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 90% and a specificity of 98%.

treatment and close follow-up. Vascular damage such as arterial stenosis, occlusion, or aneurysm may require open surgical or endovascular repair. The mortality rate among patients with TAK is increased compared with the general population. Death is often due to aortic aneurysm rupture, cardiac ischemia, or stroke.

KEY FACTS

✓ Clinical features of GCA—

  - new-onset headache and scalp tenderness in the context of a systemic inflammatory syndrome
  - jaw claudication, present in about one-third of patients, is highly specific for GCA
  - ocular symptoms may occur (eg, decreased vision, diplopia, amaurosis fugax)

✓ Treatment of GCA—

  - corticosteroids
  - begin treatment promptly (do not wait for temporal artery biopsy)
  - histopathologic evidence of arteritis persists for weeks after start of therapy

✓ TAK—

  - typically in women <40 years of age
  - nonspecific constitutional symptoms (eg, fatigue, malaise, arthralgia, myalgias)
  - extremity claudication is common

Medium Vessel Vasculitis

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis that predominantly involves medium-sized and small arteries. For most patients, the cause of PAN is unknown, but one-third of cases are related to hepatitis B virus (HBV) infection. Less commonly, PAN may occur as a paraneoplastic process, or it may be related to drug use (particularly minocycline).

Key Definition

Polyarteritis nodosa: *a systemic necrotizing vasculitis that predominantly involves medium-sized and small arteries.*

Clinical Features

For patients with PAN, the most commonly affected organs are the kidneys, skin, nerves, stomach, and intestines. Patients with PAN generally present with prominent constitutional features, such as fever, fatigue, weight loss, myalgias, and arthralgias. Peripheral neurologic symptoms are frequently present (eg, numbness, paresthesia, asymmetrical motor deficits). Skin manifestations may include livedo reticularis, tender subcutaneous nodules, palpable purpura, digital gangrene, and skin ulcerations. Abdominal pain suggests gastrointestinal tract involvement, such as mesenteric ischemia, hemorrhage, or bowel perforation. In men, testicular pain due to ischemia is a characteristic manifestation of PAN disease. Renal involvement often leads to arterial hypertension and ischemic nephropathy with renal insufficiency. Lung involvement is typically absent. Some patients have localized PAN involving a single organ such as the skin (cutaneous PAN).

Diagnosis

Abnormal laboratory findings that support a diagnosis of PAN include normocytic anemia, increased ESR and CRP level, and thrombocytosis. Testing for antineutrophil cytoplasmic antibodies (ANCAs) is typically negative. Serologic studies for chronic hepatitis should be performed because HBV infection influences treatment. The confirmatory test for PAN is either angiography or a biopsy of involved tissue (muscle, nerve, or deep skin) that shows vasculitis. Conventional arteriography is more sensitive than CTA and should include views of the renal and mesenteric arteries. Microaneurysms and stenoses of intraparenchymal arteries are characteristic angiographic findings in PAN (Figure 84.2). The classification criteria for PAN are listed in Table 84.1.

Treatment and Outcome

Prompt initiation of treatment with corticosteroids is essential to limit organ damage from vasculitis. Some patients can be treated with prednisone alone. However, in the presence of poor prognostic indicators (eg, renal insufficiency; gastrointestinal tract, cardiac, or neurologic involvement), corticosteroids are generally combined with cyclophosphamide. Methotrexate or azathioprine may be used for remission induction in less severe disease or as remission maintenance agents after a course of cyclophosphamide. For patients with HBV-related PAN,

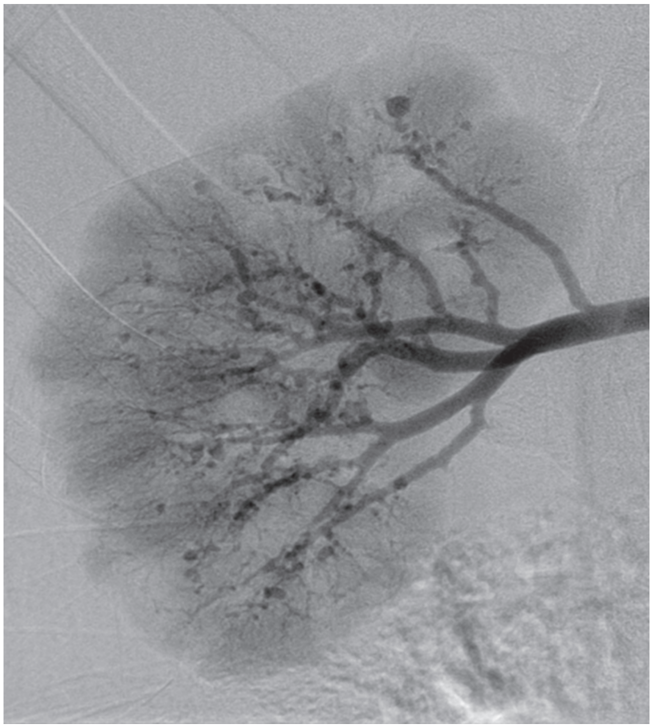

Figure 84.2. *Polyarteritis Nodosa. Renal arteriogram shows characteristic microaneurysms due to polyarteritis nodosa.*

Table 84.1 • Classification of Polyarteritis Nodosa[a]

Criterion	Definition
1. Weight loss ≥4 kg	Loss of ≥4 kg of body weight since illness began (not from dieting or other factors)
2. Livedo reticularis	Mottled reticular pattern of the skin over portions of the extremities or torso
3. Testicular pain or tenderness	Pain or tenderness of the testicles (not from infection, trauma, or other causes)
4. Myalgias, weakness, or leg tenderness	Diffuse myalgias (excluding shoulder and hip girdle), weakness of muscles, or tenderness of leg muscles
5. Mononeuropathy or polyneuropathy	Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy
6. Diastolic BP >90 mm Hg	Development of hypertension with the diastolic BP >90 mm Hg
7. Elevated BUN or creatinine level	Increase of BUN >40 mg/dL or creatinine >1.5 mg/dL (not from dehydration or obstruction)
8. Hepatitis B virus	Presence of hepatitis B surface antigen or antibody in serum
9. Arteriographic abnormality	Arteriogram showing aneurysms or occlusions of the visceral arteries (not from arteriosclerosis, fibromuscular dysplasia, or other noninflammatory causes)
10. Biopsy of small or medium-sized artery containing PMNs	Histologic changes showing the presence of granulocytes or granulocytes and mononuclear leukocytes in the artery wall

Abbreviations: BP, blood pressure; PMN, polymorphonuclear neutrophil; BUN, blood urea nitrogen.

[a] For classification purposes, a patient shall be said to have polyarteritis nodosa if at least 3 of these 10 criteria are present.

From Lightfoot RW Jr, Michel BA, Bloch DA, Hunder GG, Zvaifler NJ, McShane DJ, et al. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. Arthritis Rheum. 1990 Aug;33(8):1088-93; used with permission.

treatment consists of a short course of corticosteroids together with antiviral agents. Although untreated PAN is associated with a poor prognosis, excellent 5-year survival rates (>80%) can be achieved with appropriate immunosuppressive therapy.

Small Vessel Vasculitis

Granulomatosis With Polyangiitis, Microscopic Polyangiitis, and Eosinophilic Granulomatosis With Polyangiitis

Granulomatosis with polyangiitis (GPA) (formerly called *Wegener granulomatosis*), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) (also called *Churg-Strauss syndrome*) are primary systemic vasculitides that involve mainly small vessels. Patients with these 3 conditions often have circulating ANCAs. These antibodies are specific for antigens in neutrophil granules and monocyte lysosomes. They can be detected with immunofluorescent techniques, which produce 2 major staining patterns: cytoplasmic ANCA (c-ANCA) and perinuclear ANCA (p-ANCA). About 90% of patients with GPA have positivity for c-ANCA, and the target antigen is typically proteinase 3. Most patients with MPA and EGPA test positive for p-ANCA, owing to reactivity with myeloperoxidase (MPO). Therefore, GPA, MPA, and EGPA are collectively known as the *ANCA-associated vasculitides* (AAVs).

The incidence of AAV is approximately 10 to 20 per 1 million population per year. GPA is the most common form of AAV (incidence, 8-10 per 1 million population). These conditions occur more frequently in older adults, with peak onset at age 65 to 70 years, and they affect men and women equally. AAV is more prevalent in white persons than populations of other ethnicities.

The cause of AAV is unknown. Genetic and environmental factors, including infections, are thought to be important in disease pathogenesis. Histologically, GPA is characterized by necrotizing granulomatous vasculitis. A necrotizing granulomatous inflammation also occurs in EGPA. However, asthma and eosinophilia are prominent characteristics of EGPA that do not occur in GPA. MPA is characterized by necrotizing small vessel vasculitis without pathologic evidence of granulomatous inflammation, which helps to distinguish this condition from GPA.

Clinical Features

Most patients with AAV present with constitutional symptoms, such as fever and weight loss, in addition to symptoms related to internal organ involvement. The main clinical features of GPA can be summarized by the mnemonic ELKS: involvement of *e*ar, nose, and throat; *l*ung; *k*idney; and *s*kin. Clinical manifestations may include symptoms of sinusitis or otitis, oral ulcers, and nasal ulcers. The nasal septum may have necrosis with perforation. Patients with tracheal inflammation can present with stridor and respiratory distress. Pulmonary involvement may include pulmonary nodules or masses, whereas alveolar capillaritis causes pulmonary hemorrhage and lung infiltrates. Massive pulmonary hemorrhage can be a life-threatening manifestation of AAV. In approximately 80% of patients with GPA, glomerulonephritis develops and leads to rapidly progressive renal failure. Other manifestations of the disease may include ocular inflammation, cutaneous vasculitis, peripheral neuropathy, inflammatory arthritis, and gastrointestinal tract vasculitis.

Almost all patients with MPA have renal involvement due to rapidly progressive glomerulonephritis. Alveolar hemorrhage is also a common pulmonary manifestation. Other clinical features of MPA include cutaneous vasculitis, peripheral neuropathy, and vasculitis of the gastrointestinal tract. About 75% of patients with MPA test positive for p-ANCA (MPO).

EGPA typically has 3 main features: allergic rhinitis and asthma; eosinophilic infiltrative disease such as eosinophilic pneumonia; and systemic small vessel vasculitis. EGPA involves the lungs, peripheral nerves, skin, and, less frequently, the heart and gastrointestinal tract. Compared with GPA and MPA, EGPA typically causes less renal disease, but cardiac involvement is a frequent cause of morbidity and death. All patients with EGPA have eosinophilia (>10% eosinophils in the blood) and about 40% test positive for p-ANCA (MPO).

Diagnosis

The diagnosis of AAV requires an integration of clinical, laboratory, and histopathologic findings. Laboratory assessment should include inflammatory markers (ESR and CRP), liver and renal function, ANCA, and urinalysis with microscopy. ANCA testing is helpful in reaching the diagnosis of AAV, but some patients with small vessel vasculitis have ANCA negativity. In addition, p-ANCA that is negative for MPO antibodies is not specific for vasculitis; it can be present among patients with inflammatory bowel disease, autoimmune liver disease, connective tissue diseases, malignancies, and even drug-induced syndromes. For patients with AAV, serial measurements of ANCA over time do not correlate well with disease activity or risk of relapse.

Patients with suspected AAV should undergo chest imaging for assessment of pulmonary involvement. For patients with neurologic symptoms, nerve conduction studies should be considered to evaluate for peripheral neuropathy. Pathologic examination of involved tissue (ie, skin, muscle, nerve, lung, or kidney) is often necessary to document small vessel vasculitis. A prompt diagnosis of AAV is essential because damage to internal organs progresses rapidly and can be attenuated with appropriate therapy.

Medical Treatment

Treatment of AAV can be divided into 3 phases: induction of remission, maintenance of remission, and treatment of relapses. Although most therapeutic data come from studies of GPA, the general principles of management also apply to MPA and EGPA.

Remission induction therapy for life-threatening forms of AAV has traditionally consisted of cyclophosphamide and corticosteroids. A typical initial treatment regimen includes oral cyclophosphamide (2 mg/kg daily) in combination with prednisone (1 mg/kg daily). This regimen leads to improvement in more than 90% of patients with GPA and to complete remission in 75%. Rituximab, an anti-CD20 antibody, has now mostly replaced cyclophosphamide as the remission induction agent of choice for AAV. Randomized clinical trials have shown that rituximab is as effective as cyclophosphamide for the initial treatment of AAV.

Repeated courses of rituximab also may be given for remission maintenance, but the optimal dosing and frequency of administration have not yet been determined. Methotrexate and azathioprine are effective medications for remission maintenance; however, methotrexate is contraindicated for patients with chronic kidney disease. An alternative agent for remission maintenance is mycophenolate mofetil, although it appears to be less effective than azathioprine. Plasma exchange can increase the rate of renal recovery for patients who have acute renal failure secondary to AAV. As with other types of vasculitis, the morbidity associated with therapy is considerable, and preventive measures to minimize risk of fractures and infections are essential. In particular, patients should receive prophylaxis against *Pneumocystis jiroveci* pneumonia.

For patients with nonsevere forms of AAV, methotrexate (20-25 mg weekly) in combination with prednisone is effective for induction of disease remission. The treatment of MPA and GPA is essentially the same when major organs are involved. High-dose corticosteroid treatment alone may be adequate for EGPA, although patients with refractory disease often require additional immunosuppressive agents.

Immunoglobulin A Vasculitis

Immunoglobulin (Ig) A vasculitis (Henoch-Schönlein purpura) is characterized by IgA deposition in vessel walls. The clinical features of IgA vasculitis typically include palpable purpura, arthralgia or arthritis, abdominal pain, and hematuria due to renal disease. The vasculitic rash typically involves the lower extremities and buttocks (Figure 84.3). Gastrointestinal tract bleeding occurs in some patients. IgA vasculitis predominantly

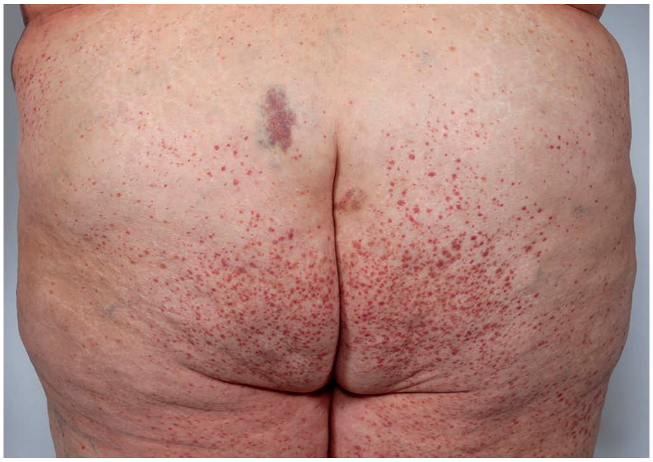

Figure 84.3. *Immunoglobulin (Ig) A Vasculitis. Cutaneous vasculitis (palpable purpura) involving the buttocks of a patient with IgA vasculitis.*

affects the pediatric population but also occurs in adults. Adult patients with IgA vasculitis have a higher risk of renal disease and should be monitored closely for this complication.

No specific biomarker for IgA vasculitis has been identified, although serum IgA levels may be elevated. The diagnosis is often clinical, and tissue biopsy (usually skin but occasionally kidney) may be required to assess for IgA deposits. In most patients, IgA vasculitis is a self-limiting condition and treatment is mainly supportive. The use of corticosteroids is controversial for this disease, but these agents should be considered for patients with abdominal pain.

KEY FACTS

✓ PAN—

- HBV infection is involved in one-third of cases
- most commonly affected organs are the kidneys, skin, nerves, stomach, and intestines
- characteristic angiographic findings are microaneurysms and stenoses of intraparenchymal arteries

✓ GPA, MPA, and EGPA—

- primary systemic vasculitides that involve mainly small vessels
- circulating ANCAs are often present

✓ GPA—90% of patients have c-ANCA positivity; the target antigen is usually proteinase 3

✓ MPA and EGPA—most patients test positive for p-ANCA, with reactivity to MPO

✓ Mnemonic for GPA clinical features—ELKS: involvement of *e*ar, nose, and throat; *l*ung; *k*idney; and *s*kin

✓ Clinical features of EGPA—

- allergic rhinitis and asthma
- eosinophilic infiltrative disease (eg, eosinophilic pneumonia)
- systemic small vessel vasculitis

✓ Agent of choice for induction of remission for AAV—rituximab has mostly replaced cyclophosphamide

✓ Clinical features of IgA vasculitis—

- palpable purpura
- arthralgia or arthritis
- abdominal pain
- hematuria due to renal disease

Cryoglobulinemia

Cryoglobulins (CGs) are immunoglobulins that precipitate at temperatures less than 37°C. A useful classification scheme for cryoglobulinemia is based on the type of CG present in the patient's serum. Type I CGs are aggregates of a single monoclonal immunoglobulin and generally are associated with hematologic malignancy, such as multiple myeloma, Waldenström macroglobulinemia, and lymphomas. Patients with type I CGs are often asymptomatic. However, type I cryoglobulinemia may cause symptoms related to hyperviscosity of the blood or thrombosis (or both). Clinical features may include headache, visual disturbances and other neurologic manifestations, Raynaud phenomenon, livedo reticularis, digital ischemia, and skin ulcerations.

Type II and type III CGs consist of more than 1 type of Ig (associated with mixed cryoglobulinemia). Type II CGs are a mixture of polyclonal Ig and a monoclonal Ig. Affected patients often test positive for rheumatoid factor. Type II CGs are mainly due to chronic viral infections (particularly hepatitis C and HIV infection), but they also can be present with autoimmune disorders and, occasionally, lymphoma. Type III CGs are polyclonal Igs and are often secondary to connective tissue diseases, such as systemic lupus erythematosus and Sjögren syndrome.

CG-containing immune complexes precipitate on endothelial cells in peripheral blood vessels and fix complement, promoting vasculitic inflammation. The typical clinical presentation includes constitutional symptoms, palpable purpura (due to leukocytoclastic vasculitis), peripheral neuropathy, and arthralgias. Less commonly, mixed cryoglobulinemia is complicated by hepatomegaly, pneumonitis or pulmonary hemorrhage, and glomerulonephritis.

Laboratory Studies

Patients with mixed CGs and small vessel vasculitis usually have an increased ESR, elevated Ig levels, a positive test for rheumatoid factor, and low levels of complement. Serum protein electrophoresis and immunoelectrophoresis are helpful in determination of the type and clonality of the Igs present. Evidence of chronic hepatitis infection (particularly hepatitis C) is often identified. For CG testing, blood must be drawn into a prewarmed syringe or collection tube; failure to prewarm the syringe or collection tube may lead to false-negative results. If CGs are detected, the laboratory also reports the cryocrit, which is a measure of the volume of the cryoprecipitate as a percentage of the original serum volume. The cryocrit does not correlate well with clinical features.

Treatment

The treatment of cryoglobulinemia depends on the disease severity and the underlying disorder. For example, patients with type I CGs require treatment of the associated hematologic malignancy. Mixed cryoglobulinemia related to chronic hepatitis C is generally treated with antiviral therapy. Patients with mixed cryoglobulinemia related to autoimmune connective tissue diseases are often treated with corticosteroids and rituximab (or cyclophosphamide), particularly when they have severe disease manifestations.

Other Forms of Vasculitis

Vasculitis may occur in association with systemic rheumatologic conditions, such as rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, Behçet disease, and sarcoidosis. The clinical manifestations of these forms of vasculitis are highly variable. Rarely, paraneoplastic vasculitis may accompany solid organ tumors or hematologic malignancies, such as lymphoma, leukemia, and myelodysplastic syndrome. For patients with hematologic malignancies, the most common presentation is a small vessel cutaneous vasculitis. Medications such as antibiotics, allopurinol, propylthiouracil, minocycline, and tumor necrosis factor inhibitors have been implicated in triggering vasculitis. Drug-induced vasculitis most often involves the skin, and internal organ manifestations are rare. Patients generally present with petechiae or palpable purpura, and skin biopsy findings include leukocytoclastic vasculitis (small vessel vasculitis with polymorphonuclear fragmentation and necrotic debris). Discontinuation of the inciting medication is often all that is necessary for management, although more severe cases may require immunosuppressive therapy.

Box 84.7 • Differential Diagnosis of Palpable Purpura

Microscopic polyangiitis
Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)
Granulomatosis with polyangiitis (formerly Wegener granulomatosis)
IgA vasculitis (Henoch-Schönlein purpura)
Cryoglobulinemic vasculitis
Vasculitis associated with rheumatic diseases (rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus)
Drug-associated vasculitis
Cancer-associated vasculitis

Abbreviation: IgA, immunoglobulin A.

The differential diagnosis for a patient presenting with palpable purpura is listed in Box 84.7.

Polymyalgia Rheumatica

PMR is an inflammatory condition that affects older persons; the mean age at diagnosis is about 73 years. The cause of PMR is unknown, although genetic and environmental factors are likely involved in disease pathogenesis. Patients with PMR typically report stiffness and pain that are most prominent in the morning and after inactivity. Symptoms generally localize to the neck, shoulders, hips, and proximal portion of the extremities. Patients often have difficulty finding a comfortable position in bed and have difficulty getting out of bed. Constitutional symptoms, such as low-grade fever, anorexia, and weight loss, are common. On musculoskeletal examination, the patients generally have painful and limited range of motion of the shoulders and hips. Extremity edema or oligoarticular synovitis can occur, particularly at the knees and wrists. Polyarticular small joint arthritis may suggest a diagnosis of elderly-onset rheumatoid arthritis rather than PMR.

No specific biomarker has been identified for the diagnosis of PMR, but classification criteria may be useful to distinguish PMR from other inflammatory disorders (Box 84.8). Patients typically have an increased ESR or CRP (or both), but autoantibodies are usually absent (eg, rheumatoid factor, cyclic citrullinated peptide antibody, antinuclear antibody). Many patients have a mild normocytic anemia, and some have a normal ESR; CRP is typically increased in these patients. Imaging is not routinely performed for the diagnosis of PMR. However, in selected cases, ultrasonography or magnetic resonance imaging may be helpful for showing articular and periarticular inflammation of the shoulders and hips.

Box 84.8 • Proposed Provisional Classification Criteria for Polymyalgia Rheumatica (PMR)[a]

Required criteria

- Age ≥50 y
- Bilateral shoulder pain
- Abnormal erythrocyte sedimentation rate or C-reactive protein level (or both)

Scoring

- Morning stiffness lasting >45 min—2 points
- Hip pain or limited range of motion—1 point
- Absence of rheumatoid factor or anti–cyclic citrullinated peptide—2 points
- Absence of other joint involvement—1 point
- Ultrasonography shows subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis in at least 1 shoulder, *and* synovitis and/or trochanteric bursitis in at least 1 hip—1 point
- Ultrasonography shows subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis in both shoulders—1 point

[a] With these clinical criteria, a score of ≥4 had a 68% sensitivity and a 78% specificity for discriminating PMR patients from comparison patients. When ultrasonographic criteria were included, a score of ≥5 had a sensitivity of 66% and a specificity of 81% for discriminating PMR patients from comparison patients.

Modified from Dasgupta B, Cimmino MA, Maradit-Kremers H, Schmidt WA, Schirmer M, Salvarani C, et al. 2012 provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Ann Rheum Dis. 2012 Apr;71(4):484-92; used with permission.

Box 84.9 • Differential Diagnosis of Patients Presenting With Polymyalgia Symptoms

Rheumatologic conditions

- Rheumatoid arthritis
- Spondyloarthropathy
- Vasculitis
- Autoimmune connective tissue diseases
- Inflammatory myopathies
- Crystalline arthritis

Musculoskeletal conditions

- Rotator cuff tendinopathy
- Greater trochanteric pain syndrome
- Degenerative joint disease
- Fibromyalgia

Other

- Thyroid disorders
- Infections (eg, disk space infection, endocarditis)
- Malignancy
- Statin-related myopathy
- Parkinsonism

Several conditions should be considered in the differential diagnosis for a patient who presents with polymyalgia symptoms (Box 84.9). Additional laboratory tests and imaging studies may be necessary to distinguish PMR from other conditions. A variant of PMR known as the **RS3PE syndrome** (ie, a syndrome of remitting seronegative symmetrical synovitis with pitting edema) occurs primarily in older men. Patients with this syndrome present with symptoms of PMR but also synovitis and marked edema of the hands or feet.

Key Definition

RS3PE syndrome: *remitting seronegative symmetrical synovitis with pitting edema; a variant of polymyalgia rheumatica that occurs primarily in older men.*

A well-recognized association exists between PMR and GCA, and experts have suggested that for some patients, PMR is an incomplete form of GCA. PMR may occur before, concurrently with, or after the onset of GCA. Clinically, 40% to 60% of patients with GCA have PMR symptoms, and GCA develops in 15% to 20% of patients who have PMR.

Treatment

Patients with PMR generally have a considerable clinical response within a few days after they begin treatment with prednisone (15-20 mg daily). For some patients, split-dose prednisone (5 mg 3 times daily) is more effective than the comparable single daily dose (15 mg once daily). The initial dose is usually maintained for 2 to 4 weeks, after which the prednisone dose may be decreased by 2.5 mg every 2 to 4 weeks until a dose of 10 mg daily is reached. Subsequently, the prednisone dose is generally tapered by 1 mg each month, although some patients may require an even slower tapering schedule. Patients should be monitored clinically, and usually ESR and CRP are measured monthly to monitor for disease activity. Disease relapses in PMR are common, and most patients require prolonged corticosteroid therapy. The typical duration of treatment is 1 to 2 years (and is sometimes longer). If polymyalgia symptoms do not improve with corticosteroids or if markers of inflammation continue to be persistently increased, alternative diagnoses should be considered. In particular, careful evaluation for GCA may need to be pursued with temporal artery biopsy or large vessel radiographic imaging (or both). Some patients with PMR are eventually reclassified as having elderly-onset rheumatoid arthritis.

KEY FACTS

✓ Clinical features of cryoglobulinemia—

- constitutional symptoms
- palpable purpura (due to leukocytoclastic vasculitis)
- peripheral neuropathy
- arthralgias

✓ Laboratory studies for cryoglobulinemia—evidence of chronic hepatitis infection (especially hepatitis C) is often identified

✓ PMR—

- inflammatory condition
- affects older persons
- mean age at diagnosis, 73 years
- stiffness and pain localized to neck, shoulders, hips, and proximal portion of extremities

✓ Treatment of PMR—

- prednisone 15-20 mg daily
- clinical response is usually evident within a few days after treatment begins

XIII

Questions and Answers

Questions

Multiple Choice (Choose the best answer)

XIII.1. A 26-year-old woman is evaluated for dyspnea. The dyspnea started 2 weeks ago and was first noticed after she jogged a mile. She takes no mediations except an occasional ibuprofen for knee pain after jogging. Her past history is important for 3 first-trimester miscarriages. On examination, the patient has a temperature of 37.3°C; blood pressure, 100/65 mm Hg; pulse, 100 beats per minute; and respiration, 14 breaths per minute. Scattered nailbed infarcts are detected on a few fingers bilaterally. The patient has no rashes. Her heart examination is notable for a grade 3/6 systolic murmur at the cardiac apex with radiation into her left axilla. Her extremities are warm, well perfused, and without edema. Laboratory results show immunoglobulin (Ig) G and IgM anticardiolipin antibodies, checked twice over a 12-week period, at 100 U/L; hemoglobin, 11.2 g/dL; white blood cell count, 10×10^9/L; and platelets, 72×10^9/L. Her erythrocyte sedimentation rate is 50 mm/hour, and creatinine is 0.9 mg/dL. A midstream urinalysis is negative for proteinuria and casts. On the basis of revised 2006 Sapporo criteria for antiphospholipid antibody syndrome (APS), the results of her examination satisfy 1 clinical criterion with history of recurrent first-trimester miscarriages and 1 laboratory criterion with high levels of IgG and IgM anticardiolipin antibodies, checked twice over 12 weeks. What is the most likely complication of her APS disease?

a. Libman-Sacks endocarditis
b. Diffuse alveolar hemorrhage
c. Glomerulonephritis
d. Pulmonary embolus

XIII.2. A 44-year-old woman presents with a 4-week history of swelling, pain, and morning stiffness in the metacarpophalangeal joints, proximal interphalangeal joints, and wrists. The patient reports an erythematous butterfly rash over her cheeks for 1 week and numerous rashes on her neck and arms that developed after she watered her garden for 10 minutes yesterday. She has fatigue and intermittently experiences pleuritic chest pain. She has been unable to work for 2 weeks. The patient's history is notable for a recent diagnosis of latent tuberculosis; she started isoniazid (INH) therapy 6 weeks ago after a purified protein derivative skin test was positive with greater than 10 mm of induration. Her history also is notable for hypertension that has been managed with hydrochlorothiazide (HCTZ) and metoprolol for 2 years without any recent medication adjustments. The patient's laboratory results are antinuclear antibody antigen of 1:640 in a homogeneous pattern; erythrocyte sedimentation test, 50 mm/hour; hemoglobin, 11.5 mg/dL, and white blood cell count, 12.2×10^9/L. What is the next best step in management?

a. Stop HCTZ therapy.
b. Prescribe hydroxychloroquine.
c. Prescribe corticosteroids.
d. Stop INH therapy.

XIII.3. A 36-year-old woman reports myriad medical symptoms and a positive antinuclear antibody (ANA) test. Her previous primary care physician has retired. During the time that the doctor monitored her, multiple tests and imaging studies had been performed without a satisfactory explanation for her problems of fatigue, headaches, paresthesias, myalgia, dizziness, depression, dry mouth, and blurry vision. Her medications are acetaminophen, tramadol, and cyclobenzaprine. Her examination shows multiple tender points in arms, back, and legs but no synovitis. Examination is otherwise normal. Laboratory investigations show a mildly positive ANA result of 1.1 units by enzyme-linked immunosorbent assay. Extractable nuclear antigen assay is negative; anti-DNA test is negative. The complement studies for C3 and C4 are normal; the complete blood cell count, chemistries, and creatinine are in the reference ranges. The most recent erythrocyte sedimentation rate (ESR) is 15 mm/hour; thyrotropin (TSH) value is 2.0 mIU/L. A midstream urinalysis is negative for proteinuria or casts. What is the most likely diagnosis in this patient?

a. Systemic lupus erythematosus (SLE)
b. False-positive ANA result
c. Sjögren syndrome
d. Drug-induced lupus

XIII.4. A 32-year-old woman presents to the clinician's office to establish care. She has a medical history of hypothyroidism and depression. She describes diffuse joint and muscle aches and pains over the past 9 months. During this same period, she has experienced fatigue, intermittent headaches, paresthesias, and unrefreshing sleep. Medications include levothyroxine. Family history is notable for a sister with undifferentiated connective tissue disorder. A review of the patient's previous workup shows values within reference levels for complete blood cell count, electrolyte panel, thyrotropin (TSH), and erythrocyte sedimentation rate. Her examination reveals no rash, lymphadenopathy, or synovitis; she does have 14 tender points. What is the next best step in management of this patient?

a. Initiation of opioid therapy
b. An antinuclear antibody (ANA) test
c. Hand radiographs
d. Initiation of milnacipran therapy

XIII.5. A 58-year-old man presents to the clinician's office with reports of right hip pain over the past 3 months. On further questioning, he describes pain in the upper, outer thigh of the right leg especially while seated for prolonged periods, along with tingling in this area. He has a history of medically complicated obesity, diabetes mellitus, hypertension, hyperlipidemia, tobacco use, osteoarthritis, and spinal stenosis. Examination shows truncal obesity, full range of motion of the right hip without serious pain or crepitus, and no focal tenderness to palpation of the low back or hip. Light touch sensation is diminished in the upper, outer thigh of the right leg. Straight-leg raise is negative bilaterally. What is the most likely diagnosis for this patient?

a. Spinal stenosis
b. Meralgia paresthetica
c. Hip osteoarthritis
d. Trochanteric bursitis

XIII.6. A 60-year-old woman presents to the clinician's office because of acute-onset low back pain for the past 2 weeks. Her medical history is important for hypertension, diabetes mellitus, a distant history of estrogen receptor–positive breast cancer with subsequent mastectomy and neoadjuvant tamoxifen, fibromyalgia, and generalized anxiety disorder. Examination shows focal tenderness to palpation along the L3 spinous process; no serious paraspinal muscle tenderness is observed at palpation. Straight-leg raise is negative bilaterally. What is the next best step in management?

a. Referral to physical therapy
b. Magnetic resonance imaging (MRI) of the lumbar spine
c. Radiograph of the lumbar spine and serum erythrocyte sedimentation rate (ESR)
d. Two-week trial of acetaminophen

XIII.7. An 82-year-old woman reports intermittent pain and swelling of her right wrist for 3 months. Onset of swelling is abrupt, lasts for a week, then remits. No other joints are involved. Her past medical history is notable for hypertension, osteoporosis, and fibromyalgia. On examination, the patient has mild warmth and swelling of the right wrist. A few bony changes are consistent with Heberden and Bouchard nodes that are nontender to palpation. No swelling of the metacarpophalangeal joints is observed. A radiograph of the right wrist shows a faint line of calcification along the triangular fibrocartilage complex. A joint arthrocentesis is performed, and under polarized microscopy, rhomboid crystals are viewed that have weak positive birefringence. What is the next best diagnostic test for this patient?

a. Calcium
b. Uric acid
c. Rheumatoid factor
d. Antinuclear antibodies

XIII.8. A 65-year-old man arrives at the emergency department in a wheelchair with acute swelling of the right first metatarsophalangeal (MTP) joint. He attended a wedding the previous night and consumed a case of beer. He woke up and could not stand on his foot because of severe pain. He has no history of trauma. The patient's past medical history is notable for poorly controlled type 2 diabetes, stage 3 chronic kidney disease, hypertension, coronary artery disease, and osteoarthritis of bilateral knees. His medications are hydrochlorothiazide, atenolol, aspirin, insulin, and acetaminophen. On examination, his temperature is 37.3°C; blood pressure, 149/50 mm Hg; and pulse, 75 beats per minute and regular. The right first MTP is red, warm, and swollen; pain to palpation is apparent, and active range of motion is limited in the first MTP joint. The right ankle is not swollen or painful. What is the next best step in treatment?

a. Oral colchicine, 1.2 mg now followed by 0.6 mg at 1 hour later
b. Oral allopurinol 300 mg daily
c. Oral prednisone 30 mg daily for 5 days
d. Intra-articular methylprednisolone

XIII.9. A 55-year-old woman reports progressive right hip pain for 6 months. The pain is most evident in her right groin when she flexes her leg, such as when she climbs into her car after working for 8 hours at an office. She has infrequent lumbar pain after lifting heavy boxes, but pain is mild and easily managed with ibuprofen. Her past medical history is notable for systemic lupus erythematosus for 15 years. She is frequently treated with bursts of methylprednisolone. Her other medications are hydroxychloroquine, ibuprofen, and a multivitamin. The examination shows a severely antalgic gait, mild tenderness over the right greater trochanter, decreased internal rotation of the right hip, and severe pain during resisted right hip flexion. A right hip radiograph shows a nearly obliterated joint space, sclerosis, and bone cysts with flattening of the right femoral head. What is the most likely diagnosis for this patient?

a. Calcium pyrophosphate dihydrate (CPPD) disease
b. Trochanteric bursitis
c. Osteonecrosis of femoral head
d. Osteoarthritis of lumbar spine

XIII.10. A 49-year-old obese woman presents with a 3-month history of hand and foot pain. She has joint swelling associated with stiffness in the mornings for about 1 hour. She has received minimal benefit with ibuprofen. Her other medication is an oral contraceptive. She drinks a glass of wine daily and has smoked cigarettes since she was a teenager. Vital signs are within normal limits. Swelling and tenderness of metacarpophalangeal joints and wrists are noted bilaterally. The patient cannot make a complete fist with either hand. Marked tenderness is present in her toes with ambulation. Laboratory results are complete blood cell count, normal; chemistry panel, normal; C-reactive protein, 3.0 mg/dL (reference range, ≤0.8 mg/dL); erythrocyte sedimentation rate, 35 mm/hour (reference range, 0-20 mm/hour); anti–cyclic citrullinated peptide antibodies, >250 U (reference range,

<20 U); and rheumatoid factor, 64 IU/mL (reference range, <24 IU/mL). Which of the following factors increased her risk of rheumatoid arthritis?

a. Oral contraception
b. Cigarette smoking
c. Alcohol use
d. Obesity

XIII.11. A 35-year-old man presents with a 3-month history of pain and swelling to the distal interphalangeal (DIP) joints of the right index and left ring fingers and diffuse swelling and pain of the right great toe. He has had an intermittent rash to the scalp and elbows since he was a teenager, which is not currently present. Laboratory investigation shows a normal complete blood cell count and blood chemistry panel. Sedimentation rate is increased at 40 mm/hour (upper limit of normal, 29 mm/hour) and C-reactive protein is increased at 10.7 mg/L (upper limit of normal, 8.0 mg/L). What is the most likely diagnosis for this man?

a. Gout
b. Lyme disease arthritis
c. Psoriatic arthritis
d. Rheumatoid arthritis

XIII.12. A 72-year-old woman with 10-lb weight loss, anorexia, fatigue, low-grade fever, and proximal muscle stiffness in her bilateral shoulders and hips received the diagnosis of polymyalgia rheumatica and started therapy with 20 mg of oral prednisone daily. She returns 2 weeks later for follow-up with resolution of low-grade temperature but only mild reduction in the proximal stiffness and fatigue. She does not endorse a headache, vision changes, scalp tenderness, or jaw claudication. Right arm blood pressure is 157/87 mm Hg; left arm blood pressure, 136/64. Laboratory findings before and after initiation of prednisone are shown in Table XIII.Q12.

Table XIII.Q12. ●

Test	Before Prednisone	14 d After Prednisone
Erythrocyte sedimentation rate	96 mm/h	84 mm/h
C-reactive protein	112 mg/L	97 mg/L
Creatinine	0.7 mg/dL	0.8 mg/dL
Leukocytes	5.9×10^9/L	14.4×10^9/L
Neutrophils	3.2×10^9/L	12.8×10^9/L

What is the next best step in treatment of this patient?

a. Temporal artery biopsy
b. Computed tomographic (CT) angiography of the aorta
c. Leukemia and lymphoma phenotyping
d. Serum protein electrophoresis

XIII.13. A 47-year-old man who emigrated from Egypt presents with malaise, fatigue, arthralgia, and painful, lower-extremity, nonblanchable purpuric lesions. He denies shortness of breath or cough. Laboratory findings show a white blood cell count of 3.7×10^9/L; platelet count, 525×10^9/L; creatinine, 1.8 mg/dL; international normalized ratio, 1.9; albumin, 2.4 g/dL; and complement C4, 6 mg/dL (reference range, 14-40 mg/dL). Urinalysis shows 21 to 30 red blood cells per high-power field and 1,248 mg of protein over 24 hours. Renal biopsy shows thickening of the glomerular basement membrane and cellular proliferation with diffuse immunoglobulin (Ig) M deposition in the capillary loops on immunofluorescence scan. Serum protein electrophoresis shows increased polyclonal IgG and monoclonal IgM κ. What is the next best step in management for this patient?

a. Antineutrophil cytoplasmic antibody (ANCA) panel for vasculitis
b. HIV-1/HIV-2 antibodies
c. Anti–glomerular basement membrane antibodies
d. Hepatitis C virus (HCV) serology

XIII.14. A 42-year-old woman with a history of hypertension, nasal polyps, chronic sinusitis, esophageal reflux, and type 2 diabetes mellitus presents with new-onset weakness and shortness of breath with exertion. Her medications are hydrochlorothiazide, metformin, aspirin, and nasal corticosteroid. Physical examination shows diffuse wheezing throughout bilateral lung fields without appreciable stridor and bilateral nasal polyps with hyperemia but no ulceration. Neurologic examination is normal except for 3/5 strength on left wrist extension and 3/5 strength on right foot dorsiflexion. Oxygen saturation on room air is 94% at rest. Chest radiography shows faint pulmonary opacities in bilateral lower lobes. Pulmonary function testing shows a forced expiratory volume in 1 second (FEV_1) to forced vital capacity ratio of 0.65 and an increase in FEV_1 by 13% following administration of a bronchodilator. White blood cell count is 6.4×10^9/L with 15% eosinophils. Antineutrophil cytoplasmic antibody (ANCA) testing is negative. Urinalysis with microscopy shows no evidence of hematuria but shows microalbuminuria. Hemoglobin A_{1c} from 6 weeks ago was 6.8%. What is the most likely diagnosis?

a. Eosinophilic pneumonitis
b. Aspirin-exacerbated respiratory disease
c. Eosinophilic granulomatosis with polyangiitis
d. Multifocal diabetic neuropathy

Answers

XIII.1. Answer a.

Libman-Sacks endocarditis is the classic cardiac manifestation of APS. This patient has clinical findings for endocarditis with a murmur and nailbed infarcts. Libman-Sacks endocarditis also is known as *nonbacterial thrombotic endocarditis*, and it most commonly involves the mitral valve. Although the patient has a mild anemia, she has no historical characteristics of hemoptysis to support a suspicion for diffuse alveolar hemorrhage. In addition, no specific aspects of her history, examination, or laboratory results suggest that she has glomerulonephritis, given her creatinine and urinalysis results. Although persons with APS are at high risk for pulmonary embolus, this patient has no clinical findings of pulmonary embolus.

XIII.2. Answer d.

This patient has drug-induced lupus (DIL) manifested by photosensitive rashes, arthralgias, and pleurisy. The correct step is to stop the INH therapy since she started it recently; INH is the most likely agent causing the DIL. Symptoms of DIL usually resolve when use of the offending agent is stopped. Although HCTZ has been associated with DIL, it is unlikely to be the cause of the patient's present symptoms because she has been taking HCTZ at a stable dose for 2 years. In some patients, low-dose corticosteroid therapy may be needed if symptoms persist after first stopping the drug therapy that was causing DIL—in this case, INH.

XIII.3. Answer b.

Aside from multiple tender points, the examination is normal. ANA is weakly positive, but specific lupus markers are absent, the complement studies are normal, and the ESR is normal. The urinalysis is normal. The most likely explanation is a false-positive ANA. The patient does not meet the criteria for the diagnosis of SLE. Although the patient reports dry mouth, she does not have dry eyes or specific characteristics on her examination to suggest Sjögren syndrome. The medications that she is taking have not been associated with causing drug-induced lupus.

XIII.4. Answer d.

This patient presents with symptoms consistent with a clinical diagnosis of fibromyalgia. Initiation of both medication and nonmedication treatment options is indicated at this time. Milnacipran, a serotonin-norepinephrine reuptake inhibitor, is an appropriate choice for treating fibromyalgia. Opioid therapy is not indicated in treatment of fibromyalgia pain. Additional testing (ANA or hand radiograph) is not warranted at this time, given the lack of concerning features and the high clinical suspicion for fibromyalgia.

XIII.5. Answer b.

This patient's presentation and examination are consistent with a clinical diagnosis of meralgia paresthetica. This condition is due to the entrapment of the lateral femoral cutaneous nerve at the level of the inguinal fold. Patients often present with reports of anterolateral thigh pain along with sensory changes (paresthesia). The presentation and examination are not consistent with spinal stenosis (predominately back pain with pseudoclaudication/radicular symptoms), hip osteoarthritis (hip and groin pain that can be reproduced with range of motion and provocative examination maneuvers), or trochanteric bursitis (lateral hip pain with focal tenderness at the trochanteric bursa).

XIII.6. Answer c.

The most appropriate next step is to obtain immediate plain radiography of the lumbar spine, and a serum ESR. According to the American College of Physicians and the American Pain Society, immediate imaging with plain radiography, as well as an ESR, is warranted for patients with acute low back pain in the clinical setting of a major risk factor for cancer (such as a history of malignancy). If the radiograph is normal but the ESR is increased, an MRI is warranted as the next step. Referral to physical therapy would be appropriate if no red-flag findings (history or examination) were present; in our case, the history is concerning enough to proceed with radiography. MRI is recommended for patients with low back pain and risk factors for spinal infection, symptoms of cauda equina syndrome, or severe or progressive neurologic deficits. Although acetaminophen could have some utility, a delay in the imaging and a possible diagnosis for a 2-week trial of analgesics is not the most appropriate management step.

XIII.7. Answer a.

A major risk factor for calcium pyrophosphate dihydrate (CPPD) is hyperparathyroidism with resulting hypercalcemia. Elevated calcium levels directly contribute to the pathogenesis of pseudogout: Tissue deposition of CPPD crystals within a joint provokes an inflammatory response. Increased levels of serum uric acid are a risk factor for gout. This patient has rhomboid crystals that are weakly positively birefringent, which are CPPD crystals. Rheumatoid arthritis rarely presents as a monoarthritis. In addition, abrupt swelling that lasts a week and then remits is much more characteristic of a crystalline arthropathy. For a woman of advanced age, systemic lupus erythematosus does not commonly present as a monoarthritis of the right wrist.

XIII.8. Answer d.

The patient has acute gout manifesting as podagra, which is treated with intra-articular injection of methylprednisolone to the right first MTP. His risk factors for gout are beer consumption, chronic kidney disease, and use of hydrochlorothiazide. Because of chronic kidney disease and diabetes, he is a candidate for a glucocorticoid injection of the right first MTP. The patient's stage 3 chronic kidney disease makes use of colchicine less desirable because of concern for severe intolerance and adverse effects. Allopurinol would be indicated as urate-lowering therapy if the patient had recurrent gout attacks over 12 months or if he had severe hyperuricemia, evidence of gouty arthropathy on radiographs, history of urate nephrolithiasis, or evidence of tophi on examination. In addition, the initial dose of allopurinol needs to be 100 mg or less when stage 3 chronic kidney disease is present. The patient has diabetes for which he takes insulin; therefore, a burst of corticosteroids is not an ideal first choice for treatment of acute gout.

XIII.9. Answer c.

The clinical presentation of right groin pain worsened with hip flexion and with reduced range of motion and radiographs that show flattening of the femoral head is most consistent with osteonecrosis of femoral head (avascular necrosis). The patient's risk factor for osteonecrosis is a history of lupus and the frequent use of glucocorticoids. Although CPPD disease may occur in the hip, the patient's clinical presentation is most consistent with osteonecrosis of femoral head (avascular necrosis). The patient has mild lumbar pain, yet this is likely mechanical low back pain from overuse.

XIII.10. Answer b.

Cigarette smoking accelerates deamination of arginine to citrulline by upregulation of peptidyl arginine deiminase 4 enzyme. Rheumatoid arthritis is believed to develop in phases, depending on the person's state of immunogenicity. The current working hypothesis is that persons with genetic predisposition (HLA-DRB1 shared epitope or other susceptibility risk loci) come in contact with an environmental trigger. This exposure then sets off a cascade of cytokine, chemokine, and autoantibody production. Citrullination (arginine converts to citrulline) appears to have a role in disease pathogenesis. Anti–cyclic citrullinated peptide antibodies typically predate the onset of rheumatoid arthritis. Oral contraception and alcohol consumption may reduce the presence of inflammatory mediators. Important research is occurring in both mucosal inflammation and the gut microbiome as contributors to rheumatoid arthritis pathogenesis.

XIII.11. Answer c.

Asymmetrical joint involvement with the DIP joints affected would be most suggestive of psoriatic arthritis. The diffuse swelling of the great toe is suggestive of dactylitis, which is a characteristic of spondyloarthropathies and is not seen with any of the other listed conditions. The rash of psoriasis may not always be present at the time of diagnosis of psoriatic arthritis. The long duration of symptoms and involvement of the upper extremities is atypical for gout. Lyme disease arthritis most often presents as monoarthritis involving the knee; in cases where there is oligoarticular involvement, the DIP joints are not usually affected. The asymmetrical joint involvement and involvement of the DIP joints is unusual for rheumatoid arthritis.

XIII.12. Answer b.

This patient has symptoms of refractory polymyalgia rheumatica. In such cases, a diagnosis of giant cell arteritis must be considered. Given the asymmetrical blood pressures, CT angiography of the aorta should be performed to determine whether the patient has aortic arch branch vessel involvement (ie, large vessel vasculitis). Temporal artery biopsy may be positive but would be considered of lower yield given the absence of cranial symptoms. The increase in leukocytes and neutrophils is due to corticosteroid use, and therefore leukemia and lymphoma phenotyping would not be beneficial. Serum protein electrophoresis would not benefit the patient's treatment at this time.

XIII.13. Answer d.

This patient presents with evidence of both nonthrombocytopenic purpura and membranoproliferative glomerulonephritis. The clinical findings raise concern for vasculitis, and the serum protein electrophoresis shows evidence of a mixed polyclonal and monoclonal protein pattern indicative of type 2 cryoglobulinemia. The most common cause of mixed cryoglobulinemia is HCV infection, and this must be excluded before treatment. The renal findings are not consistent with ANCA-associated vasculitis, which is characterized by pauci-immune glomerulonephritis. Although HIV infection has been associated with mixed cryoglobulinemia, its prevalence in this patient group is markedly lower than HCV. The lack of lung involvement makes anti–glomerular basement membrane antibody disease (Goodpasture syndrome) less likely, and the renal biopsy is not indicative of this condition.

XIII.14. Answer c.

The presence of chronic sinusitis, adult-onset asthma, pulmonary opacities, mononeuritis multiplex, and increased eosinophils make eosinophilic granulomatosis with polyangiitis the most likely diagnosis. ANCA testing is positive in only 30% to 60% of patients with this condition. Although eosinophilic pneumonitis and aspirin-exacerbated respiratory disease can have evidence of pulmonary changes, they would not account for the development of neurologic features. Multifocal diabetic neuropathy can lead to weakness in upper and lower extremities but would not explain the respiratory symptoms or the eosinophilia.

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